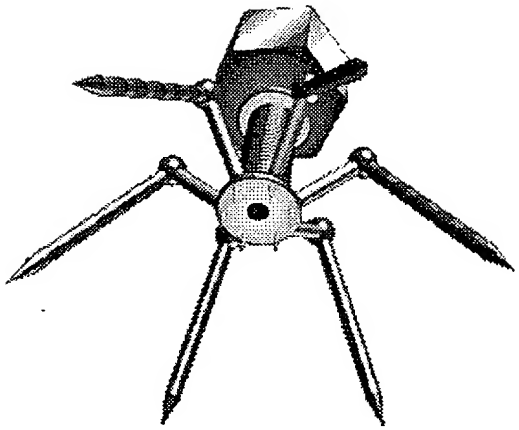

Bacteriophage Ecology Group Phage Therapy References

updated search 10/02 RB

Dedicated to the ecology and evolutionary biology of the parasites of unicellular organisms (UOPs)

contents | phage ecology group | top of page

last updated on Tuesday, December 25, 2001

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1. **Bacteriophage therapy rescues mice bacteremic from a clinical isolate of vancomycin-resistant *Enterococcus faecium*. Biswas, B., Adhya, S., Washart, P., Paul, B., Trostel, A.N., Powell, B., Carlton, R., Merril, C.R. (2002). *Infect. Immun.* 70:204-210.** Colonization of the gastrointestinal tract with vancomycin-resistant *Enterococcus faecium* (VRE) has become endemic in many hospitals and nursing homes in the United States. Such colonization predisposes the individual to VRE bacteremia and/or endocarditis, and immunocompromised patients are at particular risk for these conditions. The emergence of antibiotic-resistant bacterial strains requires the exploration of alternative antibacterial therapies, which led our group to study the ability of bacterial viruses (bacteriophages, or phages) to

rescue mice with VRE bacteremia. The phage strain used in this study has lytic activity against a wide range of clinical isolates of VRE. One of these VRE strains was used to induce bacteremia in mice by intraperitoneal (i.p.) injection of 10 9 CFU. The resulting bacteremia was fatal within 48 h. A single i.p. injection of 3 _ 10 8 PFU of the phage strain, administered 45 min after the bacterial challenge, was sufficient to rescue 100% of the animals. Even when treatment was delayed to the point where all animals were moribund, approximately 50% of them were rescued by a single injection of this phage preparation. The ability of this phage to rescue bacteremic mice was demonstrated to be due to the functional capabilities of the phage and not to a nonspecific immune effect. The rescue of bacteremic mice could be effected only by phage strains able to grow in vitro on the bacterial host used to infect the animals, and when such strains are heat inactivated they lose their ability to rescue the infected mice. [TOP OF PAGE]

2. **Phage treatment: can we utilise it for certain infective diseases in India? Bhatia, R.S. (2001).** ***Journal of the Association of Physicians of India*** **49:590** [TOP OF PAGE]

3. **Phages and their application against drug-resistant bacteria. Chanishvili, N., Chanishvili, T., Tediashvili, M., Barrow, P.A. (2001).** ***Journal of Chemical Technology and Biotechnology.*** **76:689-699.** At the beginning of the 20th century the phenomenon of spontaneous bacterial lysis was discovered independently by Twort and d'Herelle. Despite the suggestion at that time by d'Herelle that these agents might be applied to the control of bacterial diseases in the west this idea was explored in a desultory fashion only and was eventually discarded largely due to the advent of extensive antibiotic usage. However, interest was maintained in countries of the former Soviet Union where bacteriophage therapy has been applied extensively since that time. Central to this work was the Eliava Institute of Bacteriophage, Microbiology and Virology in Tbilisi, Georgia, which was founded in 1923 through the joint efforts of d'Herelle and the Georgian George Eliava. Ironically, given his contributions to public health in the

Soviet Union, Eliava was branded as an enemy of the people in 1937 and executed. d'Herelle never again returned to Georgia. In spite of these tragic events this institute remained the focus for phage therapy in the world and despite being continuously active in this field for 75 years, now struggles for its financial life. In the Eliava Institute, phages were sought for bacterial pathogens implicated in disease outbreaks in different parts of the Soviet Union and were dispatched for use in hospitals throughout the country. Although infections caused by a wide variety of bacterial pathogens have been treated, much of this has been published in Russian and is not readily available in the west. Work has also been carried out in Poland over many years and this has only recently been published in English. By contrast, interest in the west has been limited to a small number of enthusiasts and academics and until very recently little interest has been shown. The main reason that the medical and scientific communities are now beginning to take notice, is the continuing world-wide rise in the incidence of multiply-antibiotic-resistant bacterial pathogens and the absence of effective means for their control. Recent publicity over the work of the Eliava Institute has concentrated the minds of the western world on the potential for infectious disease control that bacteriophage offer, a procedure that is biologically more acceptable than antibiotic use and which has been in use for several decades already. [TOP OF PAGE]

4. **Progeny of the phage school. Dixon, B. (2001).** ***ASM News*** **69:432-433.** Frederick Twort, the eccentric polymath who discovered bacterial viruses, would have robustly welcomed the applications of bacteriophages now emergy, from therapeutics to environmental protection. [TOP OF PAGE]

5. **Phage antibacterials make a comeback. Fischetti, V.A. (2001).** ***Nature Biotechnology*** **19:734-735.** [no abstract?]. [TOP OF PAGE]

6. **H-mutant bacteriophages as a potential biocontrol of bacterial blight of geranium. Flaherty, J.E., Harbaugh, B.K., Jones, J.B., Somodi, G.C., Jackson, L.E. (2001).** ***Hortscience*** **36:98-100.** Bacteriophages

specific to *Xanthomonas campestris* pv. pelargonii (Xcp), the causal agent of bacterial blight of geranium, *Pelargonium Xhortorum* L.H. Bailey, were isolated from soil and sludge samples from Florida, California, Minnesota, and Utah. Sixteen phages were evaluated for their potential to lyse 21 Xcp strains collected from around the world. The Xcp strains varied in their susceptibility to the phage isolates with 4 to 14 phages producing a lytic or highly virulent reaction. A mixture of five h-mutants was developed from phages that exhibited the broadest host-ranges and tested against the same Xcp strains. The h-mutant phage mixture lysed all 21 Xcp strains. Three experiments were designed to determine the efficacy of using a mixture of four h-mutant phages to control the spread of the bacterial blight pathogen on potted and seedling geraniums under greenhouse conditions. Plants surrounding diseased inoculated plants were treated with a phage mixture at 5 X 108 pfu/mL daily, biweekly, or triweekly, or treated with Phyton-27(R), at 2.0 mLcntdotL-1 every 10 or 14 days. In potted geraniums, daily foliar sprays of the phage mixture had reduced disease incidence and severity by 50% and 75%, respectively, relative to control plants after 6 weeks. In two plug experiments, the phage mixture applied daily also had reduced disease incidence and severity by 69% and 86%, and 85% and 92%, respectively, when compared with controls after 5 weeks. In all three experiments, disease incidence and severity were less for plants treated daily with phages than for those treated less frequently with phages or with Phyton-27(R). Chemical name used: copper sulfate pentahydrate (Phyton-27(R)). [TOP OF PAGE]

7. **Bacteriophage therapy for bacterial infections: Rekindling a memory from the pre-antibiotics era. Ho, K. (2001). *Perspectives in Biology and Medicine* 44:1-16.** [TOP OF PAGE]

8. **Use of bacteriophage therapy in surgical practice. Lakhno, V.M., Bordunovskii, V.N. (2001). *Vestnik Khirurgii Imeni I. I. Grekova* 160:122-125.** [TOP OF PAGE]

9. **Efficacy of bacteriophage use in complex treatment of the patients**

with burn wounds. Lazareva, E.B., Smirnov, S.V., Khvatov, V.B., Spiridonova, T.G., Bitkova, E.E., Darbeeva, O.S., Mayskaya, L.M., Parphenyuk, R.L., Menshikov, D.D. (2001). ***Antibiotiki i Khimioterapiya*** **46:10-14.** Results of clinical and laboratory evaluation of the treatment with pyobacteriophage in tablets of the patients with burn wounds are presented. It was shown that phagotherapy provided more rapid cure of pyoseptic complications, temperature normalization, wounds purification and lower lethality Bacteriological analysis of wound secretions revealed that after the treatment staphylococci and streptococci were cultured 2 times rarely, *Proteus* spp. Were isolated 1.5 times rarely, *E. coli* was not isolated. The amount of positive haemocultures also diminished. Investigation of immunologic status demonstrated statistically significant normalization of immunity on cell level. Phagocytosis level didn't change while in control group (without bacteriophage use) it became lower. Antibody level enhanced but less extensively than in control group. The results of trial demonstrates positive effect of phagotherapy use at the patients with burns. [TOP OF PAGE]

10. **Examination of bacteriophage as a biocontrol method for salmonella on fresh-cut fruit: a model study. Leverentz, B., Conway, W.S., Alavidze, Z., Janisiewicz, W.J., Fuchs, Y., Camp, M.J., Chighladze, E., Sulakvelidze, A. (2001).** ***Journal of Food Protection*** **64:1116-1121.** The preparation and distribution of fresh-cut produce is a rapidly developing industry that provides the consumer with convenient and nutritious food. However, fresh-cut fruits and vegetables may represent an increased food safety concern because of the absence or damage of peel and rind, which normally help reduce colonization of uncut produce with pathogenic bacteria. In this study, we found that *Salmonella enteritidis* populations can (i) survive on fresh-cut melons and apples stored at 5 degrees C, (ii) increase up to 2 log units on fresh-cut fruits stored at 10 degrees C, and (iii) increase up to 5 log units at 20 degrees C during a storage period of 168 h. In addition, we examined the effect of lytic, Salmonella-specific phages on reducing *Salmonella* numbers in experimentally contaminated fresh-cut melons and apples

stored at various temperatures. We found that the phage mixture reduced Salmonella populations by approximately 3.5 logs on honeydew melon slices stored at 5 and 10 degrees C and by approximately 2.5 logs on slices stored at 20 degrees C, which is greater than the maximal amount achieved using chemical sanitizers. However, the phages did not significantly reduce *Salmonella* populations on the apple slices at any of the three temperatures. The titer of the phage preparation remained relatively stable on melon slices, whereas on apple slices the titer decreased to nondetectable levels in 48 h at all temperatures tested. Inactivation of phages, possibly by the acidic pH of apple slices (pH 4.2 versus pH 5.8 for melon slices), may have contributed to their inability to reduce *Salmonella* contamination in the apple slices. Higher phage concentrations and/or the use of low-pH-tolerant phage mutants may be required to increase the efficacy of the phage treatment in reducing *Salmonella* contamination of fresh-cut produce with a low pH. [TOP OF PAGE]

11. **Understanding bacteriophage therapy as a density-dependent kinetic process. Payne, R.J.H., Jansen, V.A.A. (2001). *J. Theor. Biol.* 208:37-48.** Studies of bacteriophage as therapeutic agents have had mixed and unpredictable outcomes. We argue that interpretation of these apparently paradoxical results requires appreciation of various density-dependent threshold effects. We use a mathematical model to delineate different categories of outcome, including therapy by simple inundation, by active biocontrol, and by delayed active biocontrol. Counter-intuitively, there are situations in which earlier inoculation can be less efficacious, and simultaneous inoculation with antibiotics can be detrimental. Predictions of therapeutic responses are made using formulae dependent on biologically meaningful parameters; experimental measurement of the parameters will be a prerequisite of application of the model to particular study systems. Such modelling can point to which aspects of phage biology might most fruitfully be engineered so as to enhance the viability of bacteriophage therapy. [TOP OF PAGE]

12. **Bacteriophage therapy. Sulakvelidze, A., Alavidze, Z., Morris, J.G.**

(2001). *Antimicrobial Agents and Chemotherapy* **45:649-659**. [TOP OF PAGE]

13. **Therapy of infections in cancer patients with bacteriophages. Weber-Dabrowska, B., Mulczyk, M., Górski, A. (2001). *CLIN APPL IMMUNOL REV* 1:131-134.** Cancer patients are known to be immunocompromised and susceptible to infections. We have used bacteriophages matched for specific bacterial isolates to treat antibiotic-resistant infections in those patients. Cure of infection was achived in all cases indicating very highefficacy of BP therapy. [TOP OF PAGE]

14. **Predation in the presence of decoys: An inhibitory factor on pathogen control by bacteriophages or bdellovibrios in dense and diverse ecosystems. Wilkinson, M.H.F. (2001). *J. Theor. Biol.* 208:27-36.** Several attempts have been made at the removal of specific pathogens from the intestinal microflora using either bacteriophages or "predatory" bacteria such as *Bdellovibrio* spp. To date these attempts have had mixed success. A mechanism explaining these findings based on competitive hindrance by non-prey, or decoy species is put forward. It is shown that this hindrance tends to damp out predator-prey oscillations, and therefore reduces the probability of prey extinction. Possible experiments to verify this theory are discussed. The decoy effect may play a role in any system with high densities of bacteria or other particulate matter, such as activated sludge or biofilms. [TOP OF PAGE]

15. **Integrated management of bacterial leaf spot of mungbean with bacteriophages of Xav and chemicals. Borah, P.K., Jindal, J.K., Verma, J.P. (2000). *Journal of Mycology and Plant Pathology* 30:19-21.** The population of *Xanthomonas axonopodis* pv *vignaeradiatae* (Xav) was completely eliminated from mungbean seeds by lytic action of bacteriophage (XMP-1) and streptomycin when the seeds were treated with Xav, phages and streptomycin at a ratio/concentration of 1: 60 + 300 mug ml-1. These results confirmed the synergistic action between phage (XMP-1) and streptomycin, as their combination could eradicate

Xav from mungbean seeds at a much lower concentration as compared to when used singly. Moreover, the seed treatment with phage lysate + streptomycin 300 mug ml-1 was also found most effective in checking seedling infection of mungbean by Xav. The seedling infection was 4 per cent as compared to 68 per cent in control. The percentage of seed germination was also increased to 86 per cent in comparison to 75 per cent in control. [TOP OF PAGE]

16. ***Helicobacter pylori*-antigen-binding fragments expressed on the filamentous M13 phage prevent bacterial growth. Cao, J., Sun, Y., Berglindh, T., Mellgard, B., Li, Z., Mardh, B., Mardh, S. (2000). *Biochim. Biophys. Acta* 1474:107-113.** Colonization of the human stomach by *Helicobacter pylori* is associated with the development of gastritis, duodenal ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer. *H. pylori*-antigen-binding single-chain variable fragments (ScFv) were derived from murine hybridomas producing monoclonal antibodies and expressed as a g3p-fusion protein on a filamentous M13 phage. The recombinant ScFv-phage reacted specifically with a 30-kDa monomeric protein of a *H. pylori* surface antigen preparation and by means of immunofluorescence microscopy the phage was shown to bind to both the spiral and coccoid forms of the bacterium. In vitro, the recombinant phage exhibited a bacteriocidal effect and inhibited specifically the growth of all the six strains of *H. pylori* tested. When H. pylori was pretreated with the phage 10 min before oral inoculation of mice, the colonization of the mouse stomachs by the bacterium was significantly reduced ($P<0.01$). The results suggest that genetic engineering may be used to generate therapy-effective phages. [TOP OF PAGE]

17. **Control of bacterial spot on tomato in the greenhouse and field with h-mutant bacteriophages. Flaherty, J.E., Jones, J.B., Harbaugh, B.K., Somodi, G.C., Jackson, L.E. (2000). *Hortscience* 35:882-884.** A mixture of host-range mutant (h-mutant) bacteriophages specific for tomato race 1 (T1) and race 3 (T3) of the bacterial spot pathogen, *Xanthomonas campestris* pv. *vesicatoria* (Doidge) Dye was evaluated for

biological control of bacterial spot on 'Sunbeam' tomato (*Lycopersicon esculentum* Mill.) transplants and field-grown plants for two seasons (Fall 1997 and Fall 1998). Foliar applications of bacteriophages were compared with similar applications of water (control) and of copper/mancozeb bactericides, the commonly used chemical control strategy for tomato seedling and field production. In 1997, the incidence of bacterial spot on greenhouse-grown seedlings was reduced from 40.5% (control) to 5.5% or 0.9% for bactericide- or bacteriophage-treated plants, respectively. In 1998, the incidence of bacterial spot was 17.4% on control plants vs. 5.5% and 2.7% for bactericide- and bacteriophage-treated plants, respectively, although these differences were not statistically significant at P ltoreq 0.05. Applications of bacteriophages to field-grown tomatoes decreased disease severity as measured by the area under the disease progress curve (AUDPC) by 17.5% (1997) and 16.8% (1998) compared with untreated control plants. Preharvest plant vigor ratings, taken twice during each field season, were higher in the bacteriophage-treated plants than in either bactericide-treated plants or nontreated controls except for the early vigor rating in 1998. Use of bacteriophages increased total weight of extra-large fruit 14.9% (1997) and 24.2% (1998) relative to that of nontreated control plants, and 37.8% (1997) and 23.9% (1998) relative to that of plants treated with the chemical bactericides. Chemical names used: manganese, zinc, carboxy-ethylene his dithiocarbamate (mancozeb). [TOP OF PAGE]

18. **Control of the eel (*Anguilla japonica*) pathogens, *Aeromonas hydrophila* and *Edwardsiella tarda*, by bacteriophages. Hsu, C.H., Lo, C.Y., Liu, J.K., Lin, C.S. (2000). *Journal of the Fisheries Society of Taiwan* 27:21-31.** *Aeromonas hydrophila* and *Edwardsiella tarda* are the two major pathogens of the eel, *Anguilla japonica*. The prevalent method to control the diseases is antibiotics. Long term and large scale application of the drugs results in resistance which makes disease control difficult. In the nature, bacteriophages are an important factor in controling bacterial population. The purpose of this research is to study the capability of the phages to control the pathogens in pond

water. Several bacteriophages of *A. hydrophila* and *E. tarda* were isolated from the water samples of southern Taiwan. In pure culture, the phages could reduce the host 3 orders of magnitude in 2 hr when the multiplicity of infection (moi) was above 11.5 at 25°C. In the pond water with added *A. hydrophila* to 6 X 10^5 / ml, the number dropped 250 folds at phage moi of 0.23 in 8 hr with accompanying phage multiplication to the level of 106 PFU/ml in the water. Most (85%) of the surviving hosts were still vulnerable to the phage. The resistant strains (15%) appeared to be lysogens since the culture broth of the strains could form phage plaques on *A. hydrophila*. In the case of *E. tarda*, the bacteria subsided rapidly even in the absence of phage in 48 hr in the pond water. [TOP OF PAGE]

19. **Prokaryotic gene therapy to combat multidrug resistant bacterial infection [editorial]. Norris, J.S., Westwater, C., Schofield, D. (2000). *Gene Therapy* 7:723-725.** [TOP OF PAGE]

20. **A Stalinist Antibiotic Alternative. Osborne, L. (2000). *New York Times Magazine* (Sunday, February 6), ???-???** A hoary Soviet method for fighting infections may prove invaluable in an age of antibiotic resistance. Maybe that's why pharmaceutical companies are flocking to a remote laboratory in Tbilisi. [TOP OF PAGE]

21. **Isolation of bacteriophages specific to a fish pathogen, *Pseudomonas plecoglossicida*, as a candidate for disease control. Park, S.C., Shimamura, I., Fukunaga, M., Mori, K.I., Nakai, T. (2000). *Appl. Environ. Microbiol.* 66:1416-1422.** Two types of bacteriophage specific to *Pseudomonas plecoglossicida*, the causative agent of bacterial hemorrhagic ascites disease in cultured ayu fish (*Plecoglossus altivelis*), were isolated from diseased ayu and the rearing pond water. One type of phage, which formed small plaques, was tentatively classified as a member of the family Myoviridae, and the other type, which formed large plaques, was classified as a member of the family Podoviridae. All 27 strains of *P. plecoglossicida* examined, which were isolated from diseased ayu from geographically different areas in 1991 to 1999,

exhibited quite similar sensitivities to either type of phage. One strain of *P. plecoglossicida* was highly virulent for ayu, and the 50% lethal dose (LD(50)) when intramuscular injection was used was 10(1.2) CFU fish(-1); in contrast, phage-resistant variants of this organism were less virulent (LD(50), >10(4) CFU fish(-1)). Oral administration of phage-impregnated feed to ayu resulted in protection against experimental infection with *P. plecoglossicida*. After oral administration of *P. plecoglossicida* cells of this bacterium were always detected in the kidneys of control fish that did not receive the phage treatment, while the cells quickly disappeared from the phage-treated fish. Bacterial growth in freshwater was lower in the presence of phage, and the number of phage PFU increased rapidly. These results suggest that it may be possible to use phage to control the disease caused by *P. plecoglossicida*. [TOP OF PAGE]

22. **Phage therapy: The peculiar kinetics of self-replicating pharmaceuticals. Payne, R.J.H., Phil, D., Jansen, V.A.A. (2000). *Clinical Pharmacology and Therapeutics* 68:225-230.** The specter of antibiotic-resistant bacteria has provoked renewed interest in the possible use of bacteriophages to control bacterial infections. We argue that clinical application of phage therapy has been held back by a failure to appreciate the extent to which the pharmacokinetics of self-replicating agents differ from those of normal drugs. For self-replicating pharmaceutical agents, treatment outcome depends critically on various density-dependent thresholds, often with apparently paradoxical consequences. An ability to predict these thresholds and associated critical time points is a necessity if phage therapy is to become clinically practicable. [TOP OF PAGE]

23. **Phage therapy—advantages over antibiotics? Pirisi, A. (2000). *Lancet* 356:1418** As antibiotic-resistant bacteria continue to threaten standard therapies against bacterial infections, a new breed of antimicrobials may be on the horizon. Many researchers believe that bacteriophages—viruses that only infect bacteria—are a promising potential therapy for bacterial disease treatment. [TOP OF PAGE]

24. **Effective phage therapy is associated with normalization of cytokine production by blood cell cultures. Weber-Dabrowska, B., Zimecki, M., Mulczyk, M. (2000). *Archivum Immunologii et Therapiae Experimentalis* 48:31-37.** The aim of this study was to investigate the effect of phagotherapy on tumor necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6) serum levels and the ability of blood cells to produce these cytokines in culture. Fifty one patients with long-term, suppurative infections of various tissues and organs were enrolled. The ability of cells to secrete cytokines was tested using whole blood cell cultures, unstimulated or stimulated with lipopolysaccharide (LPS) from E. coli. In addition, cytokine serum levels were determined. Measurement of cytokine activity was performed using bioassays. We showed that TNF-alpha, but not IL-6 serum levels, were regulated upon division of patients into categories exhibiting initial: low, moderate and high cytokine levels. The low spontaneous production of IL-6 by blood cell cultures was elevated significantly on day 21 of phage therapy, whereas high release of this cytokine was inhibited. No such correlation was observed with LPS-induced IL-6 production in cell cultures when cells from low-, moderately- or highly-reactive patients were studied. Phage therapy modified TNF release according to the initial ability to produce that cytokine: it reduced TNF production in high responders and increased it in low responders. Patients infected only with Gram-positive bacteria demonstrated analogous changes in the spontaneous and LPS-induced TNF-alpha production as in the whole studied group. A similar kind of regulation was observed in TNF-alpha and LPS-induced production, i.e. low production was significantly elevated, high strongly inhibited, and moderate only slightly affected. In summary, we demonstrated for the first time that effective phage therapy can normalize TNF-alpha serum levels and the production of TNF-alpha and IL-6 by blood cell cultures. [TOP OF PAGE]

25. **Bacteriophage therapy of bacterial infections: An update of our institute's experience. Weber-Dabrowska, B., Mulczyk, M., Gorski, A. (2000). *Archivum Immunologiae et Therapiae Experimentalis* 48:547-551.** 1307 patients with suppurative bacterial infections caused

by multidrug-resistant bacteria of different species were treated with specific bacteriophages (BP). BP therapy was highly effective; full recovery was noted in 1123 cases (85.9%). In 134 cases (10.9%) transient improvement was observed and only in 50 cases (3.8%) was BP treatment found to be ineffective. The results confirm the high effectiveness of BP therapy in combating bacterial infections which do not respond to treatment with the available antibiotics. [TOP OF PAGE]

26. **Viruses help fight bacteria that resist antibiotics. ??? (1999). *The Patriot Ledger Quincy, MA* 13(183?), 183? (News Section)-same?** Scientists have harnessed nature's way of tackling antibiotic- resistant bacteria. An injection of a virus that attacks bacteria only has saved the life of a patient after all other drugs proved useless. The technique -- the use of bacteriophages, or bacteria-eaters -- was pioneered in the former Soviet Union at around the time of the discovery of much more swiftly effective antibiotics. Although penicillin and other such drugs changed medicine, one team in Tbilisi, Georgia, kept research in phages going to the present day. [TOP OF PAGE]

27. **Phage therapy: past history and future prospects. Carlton, R.M. (1999). *Archivum Immunologii et Therapiae Experimentalis* 47:267-274.** Bacterial viruses (bacteriophages, also called "phages") can be robust antibacterial agents in vitro. However, their use as therapeutic agents, during a number of trials from the 1920s to the 1950s, was greatly handicapped by a number of factors. In part, there were certain limitations inherent in phage physiology (e. g. narrow host range, and rapid clearance from the body); in part there were technological limitations in the era (e.g. lysogeny not yet discovered); but the greatest limitation was the highly inadequate scientific methodologies used by practitioners at the time (e.g., their failure to conduct placebo-controlled studies, to remove endotoxins from the preparations, and to re-confirm phage viability after adding sterilizing agents to the preparations). In recent years, well-controlled animal models have demonstrated that phages can rescue animals from a variety of fatal infections, while non-controlled clinical reports published

in Eastern Europe have shown that phages can be effective in treating drug-resistant infections in humans. This encouraging data, combined with the fact that drug-resistant bacteria have become a global crisis, have created a window of opportunity for phage therapy to be tested anew, this time using modem technologies and placebo-controlled designs. If successful, it can be used as a stand-alone therapy when bacteria are fully resistant to antibiotics, and as a valuable adjunct to antibiotics when the bacteria are still susceptible. [TOP OF PAGE]

28. **Biocontrol of *Erwinia amylovora* using bacteriophage. Gill, J.J., Svircev, A.M., Myers, A.L., Castle, A.J. (1999). *Phytopathology* 89:S27** [TOP OF PAGE]

29. **Biocontrol of *Escherichia coli* O157 with O157-specific bacteriophages. Kudva, I.T., Jelacic, S., Tarr, P.I., Youderian, P., Hovde, C.J. (1999). *Appl. Environ. Microbiol.* 65:3767-3773.** *Escherichia coli* O157 antigen-specific bacteriophages were isolated and tested to determine their ability to lyse laboratory cultures of *Escherichia coli* O157:H7. A total of 53 bovine or ovine fecal samples were enriched for phage, and 5 of these samples were found to contain lytic phages that grow on *E. coli* O157:H7. Three bacteriophages, designated KH1, KH4, and KH5, were evaluated. At 37 or 4 degrees C, a mixture of these three O157-specific phages lysed all of the *E. coli* O157 cultures tested and none of the non-O157 *E. coli* or non-*E. coli* cultures tested. These results required culture aeration and a high multiplicity of infection. Without aeration, complete lysis of the bacterial cells occurred only after 5 days of incubation and only at 4 degrees C. Phage infection and plaque formation were influenced by the nature of the host cell O157 lipopolysaccharide (LPS). Strains that did not express the O157 antigen or expressed a truncated LPS were not susceptible to plaque formation or lysis by phage. In addition, strains that expressed abundant mid-range-molecular-weight LPS did not support plaque formation but were lysed in liquid culture. Virulent O157 antigen-specific phages could play a role in biocontrol of *E. coli* O157:H7 in animals and fresh foods without compromising the viability of other

normal flora or food quality. [TOP OF PAGE]

30. **Bacteriophages: An altertnative to antibiotics? Lorch, A. (1999).** ***Biotechnology and Development Monitor*** **39:14-17.** Bacterial resistance to antibiotics has become a serious medical problem. Treatment with bacteriophages might pose an effective alternative that has long been known but has been ignored outside the former Soviet Union. The development of phage therapies exemplifies positive as well as negative implications for scientific development that is restricted in its access to the mainstream, English-language dominated scientific community. [TOP OF PAGE]

31. **Protective effects of bacteriophage on experimental *Lactococcus garvieae* infection in yellowtail. Nakai, T., Sugimoto, R., Park, K.-H., Matsuoka, S., Mori, K., Nishioka, T., Maruyama, K. (1999).** ***Diseases of Aquatic Organisms*** **37:33-41.** The present study describes the *in vitro* and *in vivo* survival of *Lactococcus garvieae* bacteriophages and the potential of the phage for controlling experimental *L. garvieae* infection in yellowtail. Anti-*L. garvieae* phages persisted well in various physicochemical (water temperature, salinity, pH) and biological (feed, serum and alimentary tract extracts of yellowtail) conditions, except for low acidity. In the *in vivo*, the phage PLgY-16 was detected in the spleens of yellowtail until 24 h after intraperitoneal (i.p.) injection, or the phage was recovered from the intestine of yellowtail 3 h after the oral administration of phage-impregnated feed but undetectable 10 h later. Simultaneous administration of live *L. garvieae* and phage enhanced recovery of the phage from the spleen or intestine. The survival rate was much higher in yellowtail that received i.p. injection of the phage after i.p. challenge with *L. garvieae*, compared with that of control fish without phage injection. When fish were i.p.-injected with phage at different hours after *L. garvieae* challenge, higher protective effects were demonstrated in fish that received phage treatment at the earlier time. Protection was also obtained in yellowtail receiving phage-impregnated feed, in which fish were challenged by an anal intubation with *L. garvieae*. Anal-intubated *L. garvieae* were detected

constantly in the spleens of the control fish, while they were detected sporadically and disappeared from the phage-treated fish 48 h later. On the other hand, orally administered phage was detected at high plaque-forming units from the intestines and spleens of the phage-treated fish until 48 h later. These results indicate that intraperitoneally or orally administered anti-*L. garvieae* phage prevented fish from experimental *L. garvieae* infection, suggesting potential use of the phage for controlling the disease. [TOP OF PAGE]

32. **[Evaluation of the usefulness of new international experimental phages for typing methicillin resistant *Staphylococcus aureus* (MRSA)]. Piechowicz, L., Wisniewska, K., Galinski, J. (1999).** ***Medycyna Doswiadczalna i Mikrobiologia*** **51:31-36.** The aim of the study was to determine the usefulness of the set of experimental phages obtained from the Central Public Health Laboratory in London for typing of MRSA strains in Poland. The study was performed on 150 MRSA strains isolated from various clinical materials in various regions of the country. The set of 10 experimental phages and the international basic set of 23 phages were used for typing. The results of the study showed that 76.8% of MRSA strains were typing with the experimental set of phages. The frequency of inhibition reactions was 19.9%. Only 3.3% of the strains were nontypable with the new phages while nearly half of the studied strains were nontypable with the basic set of phages. The studied strains were divided into 19 phagotypes. There was a high frequency of typable strains among MRSA typable and nontypable strains and those inhibited by the basic set of phages (71.4%-85.7%). These data indicate that the set of 10 experimental phages is useful for typing of MRSA strains isolated in Poland except for phage M3 which failed to react with almost all the strains and should be excluded from the proposed set. [TOP OF PAGE]

33. **Prevention of Clostridium difficile-induced ileocecitis with bacteriophage. Ramesh, V., Fralick, J.A., Rolfe, R.D. (1999).** ***Anaerobe*** **5:69-78.** A bacteriophage specific for *Clostridium difficile* was examined for its ability to prevent ileocecitis in a hamster model.

This species- and strain-specific bacteriophage was isolated from a lysogenic strain of C. difficile. Hamsters were maintained in sterile isolation cages to prevent the acquisition of *C. difficile* from the environment. Bicarbonate neutralization of gastric acidity was necessary for bacteriophage survival in the hamster's gastrointestinal tract. Bacteriophage recovery from the hamster cecum was 2 X 10^4 plaque forming units/mL of cecal contents 24 h after orogastric challenge with 10^8 plaque forming units/mL of bacteriophage. However, there was no bacteriophage recovery 48 h post challenge, indicating dissipation of bacteriophage from the hamster intestinal tract within this time frame. Twenty-four hours after being challenged with clindamycin, one group of hamsters was challenged with *C. difficile* followed by a single dose of bacteriophage (10*8* plaque forming units/mL). Two additional groups of hamsters received phage doses immediately after *C. difficile* challenge and subsequently thereafter every 8 h up to 48 and 72 h, respectively. The gastric acidity was neutralized with bicarbonate buffer preceding every bacteriophage treatment. Control animals that received only clindamycin and *C. difficile* died within 96 h after challenge while the majority of bacteriophage treated hamsters survived. Two weeks after stopping bacteriophage treatment, the surviving hamsters were rechallenged with clindamycin and *C. diifficile*. All the hamsters died within 96 h indicating susceptibility of the surviving hamsters to *C. difficile* disease in the absence of bacteriophage treatment. [TOP OF PAGE]

34. **Bacteriophage therapy of *Clostridium difficile*-associated intestinal disease in a hamster model. Rdamesh, V., Fralick, J.A., Rolfe, R.D. (1999). *Miroecol. Anarobes[sic?]* 5:69-???** [TOP OF PAGE]

35. **Hospital Horror. Sardar, Z. (1999). *New Statesman* , ???-???** Our hospitals are becoming hazardous places. One can go in with a curable illness and come out with an incurable one. The risk of being infected by a "superbug", bacterial infection that is resistant to antibiotic, is very real. It has always been possible to die from surgical infection, but the arrival of superbugs has increased this risk enormously. Within ten years

most of these infections will not be treatable with antibiotics. ¶ This crisis is solely due to overuse of antibiotics. We use antibiotics as a panacea for all illnesses, and doctors have become accustomed to prescribing them as blanket coverage for all complaints. Patients, too, think antibiotics are magic bullets and demand them for every flu of every season. Worse, we use antibacterial agents in household products such as washing-up liquid, bin liners and kitchen utensils. A recent essay in Nature shows how this domestic overuse is leading to resistant bacteria. For example, E coli, one of the most common causes of food poisoning, is developing resistance to triclosan, a common antibacterial agent. ¶ That is the bad news. The good news is that there is a relatively safe and easy cure for drug-resistant strains of infectious bacteria. It's called phage therapy. Bacteriophage, or "bacteria eaters", are viruses extracted from , raw sewage. They thrive wherever bacteria thrive -- in our bodies, waste products, rivers. Phage therapy has been freely available in the former communist world for decades. Even now, a dilapidated factory in Tblisi, Georgia, is producing supplies of bacteriophage under the most difficult conditions. And we in the west, having spent astronomical sums in a vain attempt to contain killer bugs, are beginning to think about learning from them. [TOP OF PAGE]

36. **[Successful treatment with bacteriophage in purulent cerebrospinal meningitis in a newborn]. Stroj, L., Weber-Dabrowska, B., Partyka, K., Mulczyk, M., Wojcik, M. (1999). *Neurologia I Neurochirurgia Polska* 33:693-698.** The subject of this report is the case of purulent meningitis in new-born caused by *Klebsiella pneumoniae*. As the intensive antibiotic therapy turned out to be ineffective phage therapy was applied. Oral administration of specific phage preparate for the period of 5 weeks resulted in complete sterilization of cerebrospinal fluid and unquestionable improvement of child's health. However, after several ventriculopunctures some complications appeared (haemorrhage into central nervous system, extra infection). They were treated in standard way. Because of increasing internal hydrocephalus and necessity of operation, the child was sent to suitable hospital for further treatment. [TOP OF PAGE]

37. **Characterization of a *Vibrio parahaemolyticus* phage isolated from marine. Yoon, S.O., Ju, S.A., Heo, M.S., Jung, C.R., Ju, J.W. (1999). *Journal of the Korean Society for Microbiology* 34:423-433.** A novel bacteriophage, designated as VPP97, that infects the strains of *Vibiro parahaemolyticus* (hallophilic, Gram-negative bacterium) isolated most commonly from marine environments, has been discovered, and several of its properties have been determined. The plaques were clear and sized 0.6-1.0 mm in diameter. The virion forms a single band on 70% sucrose gradient and p1.50 CsCl gradient by sucrose gradient centrifugation and CsCl gradient centrifugation respectively. It has a hexagonal head and a relatively long tail, as shown by electron microscopy. *Vibrio alginolyticus, Vibrio fluvialis* and *Vibrio furnissii* were also sensitive to this phage It was almost totally inactivated at 70°C and at pH below 5 or over 10. The nucleic acid of VPP97 is composed of DNA. The VPP97 had 9 specific structural proteins sized between 21.5 kDa and 97.4 kDa on SDS-PAGE. When *V. parahaemolyticus* cultures were treated with either phage VPP97 or one of the several antibiotics for 2 hours, the viable number of *V. parahaemolyticus* treated with the phage VPP97 is lower than that treated with chloramphenicol, erythromycin or penicillin, but not lower than that treated with tetracycline. Mice that have responded to the phage treatment revealed the lower numbers of *V. parahaemolyticus* in small intestine and less damage on small intestine compared to the untreated mice. Therefore, we suggest that the phage treatment appears effective to the infection by *V. parahaemolyticus*. [TOP OF PAGE]

38. **Practical use of adapted *Salmonella bacteriophage* for the treatment and prophylaxis of nosocomial salmonellosis. Akimkin, V.G., Bondarenko, V.M., Voroshilova, N.N., Darbeeva, O.S., Baiguzina, F.A. (1998). *Zhurnal Mikrobiologii Epidemiologii i Immunobiologii* 85-86.** [TOP OF PAGE]

39. **Ispol'zovanie adaptirovannogo sal'monelleznogo bakteriofaga v praktike lecheniia i profilaktiki nozokomial'nogo sal'monelleza**

[Practical use of adapted *Salmonella* bacteriophage for the treatment and prevention of nosocomial infections]. Akimkin, V.G., Bondarenko, V.M., Voroshilova, N.N., Darbeeva, O.S., Baiguzina, F.A. (1998). *Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii* 85-86. [TOP OF PAGE]

40. **Bacteriophages show promise as antimicrobial agents. Alisky, J., Iczkowski, K., Rapoport, A., Troitsky, N. (1998). *J. Infect.* 36:5-15.** The emergence of antibiotic-resistant bacteria has prompted interest in alternatives to conventional drugs. One possible option is to use bacteriophages (phage) as antimicrobial agents. We have conducted a literature review of all Medline citations from 1966-1996 that dealt with the therapeutic use of phage. There were 27 papers from Poland, the Soviet Union, Britain and the U.S.A. The Polish and Soviets administered phage orally, topically or systemically to treat a wide variety of antibiotic-resistant pathogens in both adults and children. Infections included suppurative wound infections, gastroenteritis, sepsis, osteomyelitis, dermatitis, empyemas and pneumonia; pathogens included *Staphylococcus*, *Streptococcus*, *Klebsiella*, *Escherichia*, *Proteus*, *Pseudomonas*, *Shigella* and *Salmonella* spp. Overall, the Polish and Soviets reported success rates of 80-95% for phage therapy, with rare, reversible gastrointestinal or allergic side effects. However, efficacy of phage was determined almost exclusively by qualitative clinical assessment of patients, and details of dosages and clinical criteria were very sketchy. There were also six British reports describing controlled trials of phage in animal models (mice, guinea pigs and livestock), measuring survival rates and other objective criteria. All of the British studies raised phage against specific pathogens then used to create experimental infections. Demonstrable efficacy against *Escherichia*, *Acinetobacter*, *Pseudomonas* and *Staphylococcus* spp. was noted in these model systems. Two U.S. papers dealt with improving the bioavailability of phage. Phage is sequestered in the spleen and removed from circulation. This can be overcome by serial passage of phage through mice to isolate mutants that resist sequestration. In conclusion, bacteriophages may show promise for treating antibiotic resistant

pathogens. To facilitate further progress, directions for future research are discussed and a directory of authors from the reviewed papers is provided. [TOP OF PAGE]

41. **Use of lytic bacteriophage for control of experimental *Escherichia coli* septicemia and meningitis in chickens and calves. Barrow, P., Lovell, M., Berchieri, A.jr. (1998). *Clin. Diag. Lab. Immunol.* 5:294-298.** A lytic bacteriophage, which was previously isolated from sewage and which attaches to the K1 capsular antigen, has been used to prevent septicemia and a meningitis-like infection in chickens caused by a $K1^+$ bacteremic strain of Escherichia coli. Protection was obtained even when administration of the phage was delayed until signs of disease appeared. The phage was able to multiply in the blood. In newly borne colostrum-deprived calves given the E. coli orally, intramuscular inoculation of phage delayed appearance of the bacterium in the blood and lengthened life span. With some provisos there is considerable potential for this approach to bacterial-disease therapy. [TOP OF PAGE]

42. **Biological control of bacterial blight of geranium with h-mutant bacteriophages. Harbaugh, B.K., Jones, J.B., Jackson, L.E., Somodi, G., Flaherty, J.E. (1998). *Hortscience* 33:519** [TOP OF PAGE]

43. **Reassessment of medicinal phage……. Holzman, D. (1998). *ASM News* 64:620-622.** [TOP OF PAGE]

44. **Phage as antibacterial tool. Holzman, D. (1998). *Genetic Engineering News* 18(18), 1-48.** [TOP OF PAGE]

45. **…Spurs companies to study therapeutic uses. Holzman, D. (1998). *ASM News* 64:622-623.** [TOP OF PAGE]

46. **Control of bacterial spot on tomato in the greehouse and field with bacteriophages. Jones, J.B., Somodi, G.C., Jackson, L.E., Harbaugh, B.K. (1998). Paper 5.2.14. Edinburgh, Scotland, 7th**

International Congress of Plant Pathology. [TOP OF PAGE]

47. **The hunt is on for new ways to overcome bacterial resistance. Knudson, M. (1998). *Technology Review* 100:22-30?** Researchers from various pharmaceutical companies are employing high technology approaches to develop ways to address disease-causing microbes that mutate to resist conventional antibiotics. [TOP OF PAGE]

48. **Return of a killer. Koerner, B.I. (1998). *U.S.News and World Report* (November 2, 1998), 51-52.** Phages may once again fight tough bacterial infections. [TOP OF PAGE]

49. **Phage therapy. Soothill, J.S. (1998). *Journal Of Pharmacy And Pharmacology* 50:36-36.** [TOP OF PAGE]

50. **Bacteriophage therapy and prophylaxis: Rediscovery and renewed assessment of potential. Barrow, P.A., Soothill, J.S. (1997). *Trends in Genetics* 5:268-271.** Bacteriophages were discovered 82 years ago. Claims for their use in the treatment of infections were not confirmed by early controlled trials, and the success of antibiotics superseded this potential use. However, recent studies have shown interesting therapeutic effects that warrant further investigation and development. [TOP OF PAGE]

51. **Infection and removal of L-forms of *Listeria monocytogenes* with bred bacteriophage. Hibma, A.M., Jassim, S.A., Griffiths, M.W. (1997). *Int. J. Food Microbiol.* 34:197-207.** Phage breeding was employed to produce a bacteriophage (Listeria monocytogenes phage ATCC 23074-B1) which was specific for L-forms of L. monocytogenes. The bred phage was compared to its unbred parent for lytic activity and specificity. It was also tested for its ability to prevent L-form biofilm formation on stainless steel and compared with an organic acid (lactic) at L-form biofilm inactivation on stainless steel. The bred phage lysed only L-forms of L. monocytogenes in broth culture and only plaqued on L-form lawns. Likewise, the unbred phage performed similarly with classical

cell-walled culture and lawns. The bred phage successfully inhibited L-form biofilm formation on stainless steel and was as successful as lactic acid (130 ppm) at inactivating pre-formed L-form biofilms. Both reduced viable cell numbers by 3-long cycles over a 6 h period. It appears that phage breeding technology may be an attractive alternative to chemical sanitizers which lack specificity and can be toxic. [TOP OF PAGE]

52. **[The study on biology of bacteriophages and their usage in the treatment of bacterial diseases and on the influence of different bacteriophages on cytokine production by leukocytes in human peripheral blood]. Kozminska, J., Weber-Dabrowska, B., Mulczyk, M. (1997).** ***OTOLARYNGOLOGIA POLSKA*** **51 Suppl 25:195-198.** The authors showed the examinations of the biology bacteriophages and using them in the treatment of the bacteriology infection and influence difference bacteriophages in producing cytokinins by leukocytes of human peripheral blood. [TOP OF PAGE]

53. **Control of Erwinia amylovora by mixtures of bacteriophage. Palmer, E.L., Fernando, W.G.D., Jones, A.L. (1997).** ***Phytopathology*** **87:S73-S74** [TOP OF PAGE]

54. **Control of bacterial spot of tomato in transplant production using h-mutant bacteriophage and a hrp- strain of Xanthomonas campestris pv. vesicatoria. Somodi, G.C., Jones, J.B., Jackson, L.E. (1997).** ***Phytopathology*** **87:S92** [TOP OF PAGE]

55. **Viral control of** ***Emiliania huxleyi*** **blooms? Bratbak, G., Wilson, W., Heldal, M. (1996).** ***J. Mar. Syst.*** **9:75-81.** [TOP OF PAGE]

56. **One infection cures another. Brown, P. (1996).** ***New Scientist*** **???, ???-???** [TOP OF PAGE]

57. **Host-dependent modification/restriction and therapeutic potential of Pseudomonas phage. Gachechiladze, K.K., Adamia, R.S.,**

Balardshishvili, N.S., Chanishvili, T.G., Kruger, D.H. (1996). Jerusalem (Israel). Xth International Congress of Virology. 1996.[TOP OF PAGE]

58. **Smaller fleas ... ad infinitum: therapeutic bacteriophage redux. Lederberg, J. (1996).** ***Proc. Natl. Acad. Sci. USA*** **93:3167-3168.** [TOP OF PAGE]

59. **Phage therapy revisited: the population biology of a bacterial infection and its treatment with bacteriophage and antibiotics. Levin, B.R., Bull, J.J. (1996).** ***Am. Nat.*** **147:881-898.** [TOP OF PAGE]

60. **Long-circulating bacteriophage as antibacterial agents. Merril, C.R., Biswas, B., Carlton, R., Jensen, N.C., Creed, G.J., Zullo, S., Adhya, S. (1996).** ***Proc. Natl. Acad. Sci. USA*** **93:3188-3192.** The increased prevalence of multidrug-resistant bacterial pathogens motivated us to attempt to enhance the therapeutic efficacy of bacteriophages. The therapeutic application of phages as antibacterial agents was impeded by several factors: (i) the failure to recognize the relatively narrow host range of phages; (ii) the presence of toxins in crude phage lysates; and (iii) a lack of appreciation for the capacity of mammalian host defense systems, particularly the organs of the reticuloendothelial system, to remove phage particles from the circulatory system. In our studies involving bacteremic mice, the problem of the narrow host range of phage was dealt with by using selected bacterial strains and virulent phage specific for them. Toxin levels were diminished by purifying phage preparations. To reduce phage elimination by the host defense system, we developed a serial- passage technique in mice to select for phage mutants able to remain in the circulatory system for longer periods of time. By this approach we isolated long-circulating mutants of *Escherichia coli* phage lambda and of *Salmonella typhimurium* phage P22. We demonstrated that the long-circulating lambda mutants also have greater capability as antibacterial agents than the corresponding parental strain in animals infected with lethal doses of bacteria. Comparison of the parental and mutant lambda

capsid proteins revealed that the relevant mutation altered the major phage head protein E. The use of toxin-free, bacteria-specific phage strains, combined with the serial-passage technique, may provide insights for developing phage into therapeutically effective antibacterial agents. [TOP OF PAGE]

61. **The good virus. The use of bacteriophages to fight antibiotic-resistant bacterial diseases. Radetsky, P. (1996).** ***Discover*** **17(11), 50-58.** Interest in bacteriophage therapy is re-emerging as antibiotic resistance grows among bacterial diseases. Bacteriophage, viruses that can kill bacteria, were discovered by Felic d'Herelle in 1917. Bacteriophage therapy virtually ended with the discovery of antibiotics in the 1940s. [TOP OF PAGE]

62. **Viruses as biological control agents for blooms of marine phytoplankton. Suttle, C.A. (1996).** pp. **71-76.** In Anonymous***Proceedings of the Brown Tide Summit, 20-21 October, 1995.*** **New York Sea Grant Institute???,** [TOP OF PAGE]

63. **Pitting Microbe against Microbe. Talan, J. (1996).** ***Newsday*** **???,** **???-???** [TOP OF PAGE]

64. **Biological warfare: Scientists once again advocate pitting viruses against bacterial infections. Travis, J. (1996).** ***Science News*** **(149), 350-???** [TOP OF PAGE]

65. **Phagotherapy of nosocomial strains of *P. aeruginosa*, belonging to the o-groups. Gabisonia, T.G., others??? (1995).** ***Georg. Med. News. (I suspect this is "Georgia Medical News" and I also suspect this is Georgia as in the former USSR)*** **N.15:19-21.** [TOP OF PAGE]

66. **Biocontrol of bacterial blotch of the cultivated mushroom with lytic phages: Some practical considerations. Munsch, P., Olivier, J.M. (1995).** pp. **595-602.** In In **Elliott, T.J. (ed.),** ***Science and Cultivation of Edible Fungi, Vol. II: Proceedings of the 14th International***

Congress. [TOP OF PAGE]

67. **[The efficacy of bacteriophage preparations in treating inflammatory urologic diseases]. [Russian]. Perepanova, T.S., Darbeeva, O.S., Kotliarova, G.A., Kondrat'eva, E.M., Maiskaia, L.M., Malysheva, V.F., Baiguzina, F.A., Grishkova, N.V. (1995).** ***Urologiia i Nefrologiia*** **14-17.** Urinary infection is the most commonly encountered hospital infection. Antibacterial therapy promotes selection and dissemination of polyresistant microorganism strains, development of intestinal dysbacteriosis, reduction of intestinal contamination resistance. Clinical and bacteriological efficacy of urinary infection treatment with bacteriophage preparations (pyocyanic, proteus, staphylococcal, coliphage, combined pyobacteriophage) was studied. Sensitivity of the infective agent phage isolated from urological patients was tested before treatment. The preparations were adapted to recently isolated agents from urological patients to raise phage sensitivity of the strains. A total of 293 strains were studied. Phage sensitivity made up 68.9%. Bacteriophage preparations were used both locally and orally in 46 patients with acute and chronic urogenital inflammation. Bacteriological efficacy amounted to 84%, clinical one to 92%. It is inferred that phagotherapy is effective and safe therapeutic modality in the treatment of urinary infection in monotherapy and in combination with antibiotics. [TOP OF PAGE]

68. ***Pseudomonas aeruginosa*** **bacteriophage in treatment of** ***P. aeruginosa*** **infetion in cystic fibrosis patients. Shabalova, I.A., Karpanov, N.I., Krylov, V.N., Sharibjanova, T.O., Akhverdijan, V.Z. (1995). 443. Zurich, Switzerland, International Cystic Fibrosis Association. Proceedings of IX International Cystic Fibrosis Congress.** [TOP OF PAGE]

69. **Bacteriophage: A smart alternative to antibiotics? Dixon, B. (1994).** pp. **190-192.** In Anonymous ***The Power Unseen.*** **W.H.Freeman/Spektrum, Oxford, UK.** [TOP OF PAGE]

70. **[Bacteriophage therapy in the treatment of recurrent subphrenic and subhepatic abscess with jejunal fistula after stomach resection]. [Polish]. Kwarcinski, W., Lazarkiewicz, B., Weber-Dabrowska, B., Rudnicki, J., Kaminski, K., Sciebura, M. (1994).** ***Polski Tygodnik Lekarski*** **49:535-535.** The case of recurrent subphrenic abscess with the jejunal fistula after stomach resection in 41-years old male is presented. In microbiological examination E. coli antibiotic-resisted was discovered. The bacteriophages were prepared and administered to the patient. The operation was performed without any antibiotics. During the whole stay at hospital the patient had got bacteriophages. He left the hospital in 33rd day of stay without any abscesses. [TOP OF PAGE]

71. **Bacteriophages in industrial fermentations. Saunders, M.E. (1994).** pp. **116-121.** In In **Webster, R. and Granoff, A.** (eds.), ***Encyclopedia of Virology.*** **Academic Press, ???** [TOP OF PAGE]

72. **Bacteriophage prevents destruction of skin grafts by *Pseudomonas aeruginosa*. Soothill, J.S. (1994).** ***Burns*** **20:209-211.** Infection of split skin grafts in guinea-pigs by *Pseudomonas aeruginosa* 3719 destroys them, and bacteriophage BS24, lytic for strain 3719, protects the grafts. This supports the view that phage could be used to prevent infection of skin grafts applied to the contaminated wounds of burned patients. ["Demonstrated that destruction of small skin grafts to guinea pigs by *P. aeruginosa* could be prevented by the prophylactic application of phage. suggesting that phage could be used to prevent infection of skin graphs applied to contaminated wounds of burns patients." Quoted from Barrow & Soothill, 1997]. [TOP OF PAGE]

73. **Xanthomonas campestris pv. pruni bacteriophages on peach trees and their potential use for biological control. Zaccardelli, M., Saccardi, A., Gambin, E., Minardi, P., Mazzucchi, U., Lemattre, M., Freigoun, S., Rudolph, K., Swings, J.G. (1994).** ***Colloques de l'INRA*** **875-878.** [TOP OF PAGE]

74. **Biological control of mushroom bacterial blotch with bacteriophages.**

Munsch, P., Olivier, J.M., Fritig, B., Legrand, M.E. (1993). *Developments in Plant Pathology* 469 [TOP OF PAGE]

75. **Bacteriophagotherapy and enterosorbtion in treatment of sepsis of newborns caused by gram-negative bacteria. Pavlenishvili, I., Tsertsvadze, T. (1993). *Pren. Neon. Infect.* 11:104-??? [TOP OF PAGE]**

76. **A biocontrol agent for Pseudomonas solanacearum. Wall, G.C., Sanchez, J.L., Hartman, G.L., Hayward, A.C. (1993). *ACIAR Proceedings* 320-321. [TOP OF PAGE]**

77. **[Immunobiological properties and therapeutic effectiveness of preparations from Klebsiella bacteriophages]. [Russian]. Bogovazova, G.G., Voroshilova, N.N., Bondarenko, V.M., Gorbatkova, G.A., Afanas'eva, EV, Kazakova, T.B., Smirnov, V.D., Mamleeva, A.G., Glukharev, I., Erastova, E.I. (1992). *Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii* 30-33.** The purified preparations of Klebsiella bacteriophages, viz. the monovalent preparation of K. pneumoniae bacteriophage and the polyvalent bacteriophage preparation for the treatment of infections caused by K. ozaenae, K. rhinoscleromatis scleromatis and K. pneumoniae sensu lato, have been obtained. The bacteriophage preparations have proved to be nontoxic and safe for laboratory animals after the intraperitoneal injection of these preparations followed by the pathomorphological study of the internal organs of the animals. The clinical study of the newly developed bacteriophage preparations in the course of the treatment of purulent inflammatory diseases in 109 patients has revealed that the preparations are not reactogenic and exhibit sufficient effectiveness in the therapy of ozena, rhinoscleroma and Klebsiella infections with different localization of the infectious process. [TOP OF PAGE]

78. **Use of polyvalent phage for reduction of *Streptomycetes* on soil dilution plates. Kurtboke, D.I., Chen, C.F., Williams, S.T. (1992). *J. Appl. Bacteriol.* 72:103-111.** An isolation method was developed in

which prior to inoculation soil suspensions were exposed to suspensions of polyvalent phage isolated to *Streptomyces* spp. The phage susceptibility of streptomycetes provided a selective means of reducing streptomycetes on isolation plates subsequent to inoculation, and this reduction was persistent after long incubation periods. The efficiency and applicability of the method developed were checked with different samples from a range of sources. The increased chances of development of other genera after the reduction of streptomycetes on soil dilution plates were assessed. [TOP OF PAGE]

79. **Characteristics and diffusion in the rabbit of a phage for Escherichia coli 0103. Attempts to use this phage for therapy. Reynaud, A., Cloastre, L., Bernard, J., Laveran, H., Ackermann, H.W., Licois, D., Joly, B. (1992). *Veterinary Microbiology* 30:203-212.** A bacteriophage for Escherichia coli 0103 was isolated during a study on E. coli diarrhoea in intensive breeding units of rabbits. The phage had an isometric head and a short tail and resembled coliphage N4 (Podoviridae). It had a very narrow host range and seemed to be specific for serogroup 0103, suggesting that it might be used for preliminary identification of E. coli strains of this serogroup instead of the usual slide agglutination. In view of its possible use as a therapeutic phage, we investigated its dissemination in rabbit organs after oral administration. The phage persisted in the spleen for at least 12 days. However, in vivo studies showed that this phage and a mixture of more virulent phages for E. coli 0103 were ineffective in preventing disease in rabbits inoculated with an enteropathogenic strain of E. coli 0103. [TOP OF PAGE]

80. **Treatment of experimental infections of mice with bacteriophages. Soothill, J.S. (1992). *J. Med. Microbiol.* 37:258-262.** Bacteriophages for *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were tested in experimental infections of mice to investigate their potential for the treatment of infections of man. As few as 10(2) particles of an acinetobacter phage protected mice against 5 LD50 (1 x 10(8)) of a virulent strain of *A. baumanii*, and phage was

demonstrated to have multiplied in the mice. A pseudomonas phage protected mice against 5 LD50 of a virulent strain of *P. aeruginosa*, with a PD50 of 1.2 x 10(7) particles. A staphylococcal phage failed to protect mice infected with a strain of *S. aureus*. These studies support the view that bacteriophages could be useful in the treatment of human infections caused by antibiotic-resistant strains of bacteria. [TOP OF PAGE]

81. **The activity in the chicken alimentary tract of bacteriophages lytic for *Salmonella typhimurium*. Berchieri, A., Lovell, M.A., Barrow, P.A. (1991). *Res. Microbiol.* 142:541-549.** Bacteriophages lytic for Salmonella typhimurium were isolated in considerable numbers from chickens experimentally infected with S. typhimurium, and in much lower numbers from the chicken feed. Lytic phages were also regularly isolated from human sewerage systems. One of these was used to inoculate S. typhimurium--infected two day-old chickens orally and via the feed. The phage took longer to establish in the caeca than did the Salmonella and it disappeared when the caecal S. typhimurium counts fell to 10(6) CFU/ml. No neutralizing antibodies to the phage were detected in the serum of these chickens. In a second experiment, five of 30 chickens similarly infected with S. typhimurium were inoculated with the phage. Within 3 days, the phage was isolated from 72% of the "in-contact" birds. A second phage, isolated from sewage, when inoculated into newly-hatched chickens simultaneously with any of 3 strains of S. typhimurium, produced a considerable reduction in mortality in the birds. This effect was only produced by inoculation of high concentrations of phage (greater than 10(10) PFU/ml). The phage produced reductions in the viable numbers of S. typhimurium in the crop, small intestine and caeca for up to 12 h after inoculation, with smaller reductions in bacterial numbers in the liver at 24 and 48 h after infection. ["Extended work on veterinary diarrhoea to *Salmonella* in poultry. . . Fewer chicks died . . . when . . . phages were given orally soon after the bacteria were administered." Quoted from Barrow & Soothill, 1997]. [TOP OF PAGE]

82. **Effektivnost' bakteriofaga Klebsiella pneumoniae pri terapii**

eksperimental'noi klebsielleznoi infektsii.[The efficacy of Klebsiella pneumoniae bacteriophage in the therapy of experimental Klebsiella infection]. [Russian]. Bogovazova, G.G., Voroshilova, N.N., Bondarenko, V.M. (1991). ***Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii*** **4:5-8.** The effectiveness of specific phage therapy was studied on Klebsiella experimental sepsis in noninbred white mice, caused by the intraperitoneal injection of K. pneumoniae highly virulent strain K2 5055 into the animals. For treatment, Klebsiella polyvalent bacteriophage administered on day 2 after the infection of the animals with Klebsiella was used. The study revealed that bacteriophage could be detected in the blood and internal organs of the animals within 24 hours irrespective of the route of its administration: intraperitoneal, intravenous or intranasal. The bacteriophage preparation, introduced intraperitoneally, was shown to be effective in the treatment of generalized Klebsiella infection. One daily intraperitoneal injection of Klebsiella bacteriophage for 15-20 days proved to be the optimum scheme of treatment. In contrast to chemotherapeutic preparations, bacteriophages had no effect on normal microflora and did not aggravate dysbiotic disturbances. For this reason, bacteriophages may become one of alternative antimicrobial remedies, selectively affecting infective agents. [TOP OF PAGE]

83. **Host-controlled modificaiton and restriction as a criterion of evaluating the therapeutical potential of *Pseudomonas* phage. Gachechiladze, K.K., others??? (1991).** ***J. Basic Microbiol.*** **31:101-106.** [TOP OF PAGE]

84. **EXPERIMENTAL CONTROL OF BACTERIAL BLOTCH BY BACTERIOPHAGES. Munsch, P., OLIVIER, J.L., HOUDEAU, G. (1991).** ***35891/MAHER, M. J. (ED.). MUSHROOM SCIENCE, VOL. XIII. SCIENCE AND CULTIVATION OF EDIBLE FUNGI, VOLS. 1 AND 2; 13TH INTERNATIONAL CONGRESS, DUBLIN, IRELAND, SEPTEMBER 1-6, 1991. XX+442P. (VOL. 1); IX+403P. (VOL. 2) A. A. BALKEMA: ROTTERDAM, NETHERLANDS; BRO*** **389-396.** [TOP OF PAGE]

85. **The virus that eats bacteria. Radetsky, P. (1991).** pp. **74-88.** In Anonymous ***The Invisible Invaders: The Story of the Emerging Age of Viruses*****. Little Brown & Company, Boston.** [TOP OF PAGE]

86. **The combined use of specific phages and antibiotics in different infectious allergoses. Sakandelidze, V.M. (1991).** ***Vrach. Delo*** **3:60-63.** [TOP OF PAGE]

87. **Pathomorphological evaluation of therapeutic effect of mycophages in tuberculosis. Zemskova, Z.S., Dorozhkova, I.R. (1991).** ***Probl. Tuberk.*** **11:63-66.** [TOP OF PAGE]

88. **Bacteriophage therapy of pseudomonas burn wound sepsis. Abdul-Hassan, H.S., El-Tahan, A., Massoud, B., Gommaa, R. (1990).** ***Annals of the Mediterranean Burn Club*** **3, 4:262-264.** [TOP OF PAGE]

89. **Inability of a bacteriophage pool to control beef spoilage. Greer, G.G., Dilts, B.D. (1990).** ***Int. J. Food Microbiol.*** **10:331-342.** The biological control of beef spoilage, with a bacteriophage (phage) pool, was evaluated under simulated retail conditions. A pool of seven phages was selected with the potential to lyse 78% of 86 *Pseudomonas* test strains. Subsequent host range studies with 1023 pseudomonads from three meat species (beef, pork, lamb) and five abattoirs showed that 585 (57.2%) isolates were susceptible to the phage pool. Depending on bacterial origin, bacterial sensitivity to lysis by the phage pool varied from 25 to 72%. When added to ribeye steaks, the phage pool produced a significant reduction in *Pseudomonas* growth but this was not sufficient to produce any significant effect upon the retail shelf life of beefj. The inability of phages to control beef spoilage was not attributed to a loss of phage virulence since sufficient densities (log pfu/cm^2 - 5 to 6) of virulent phage could be re-isolated from beef, 14 days after treatment. It was concluded that the efficacy of the current phage pool was limited by a narrow range of specificity. [TOP OF PAGE]

90. **Use of bacteriophages and antibiotics for prevention of acute postoperative empyema in chronic suppurative lung diseases. Kaczowski, H., Weber-Dabrowska, B., Dabrowski, M., Zdrojweicz, Z., Cwioro, F. (1990). *Wiad. Lek.* 43:136-141.** [TOP OF PAGE]

91. **USE OF ECOLOGICALLY HARMLESS PESTICIDES IN CROP INDUSTRY ITS STATUS PROBLEMS AND PROSPECTS REPORT 2. PATHOGEN OF FUNGAL AND BACTERIAL DISEASES. SOKOLOV, M.S. (1990). *Agrokhimiya* 124-145.** [TOP OF PAGE]

92. **CONTROL OF TOBACCO BACTERIAL WILT BY AN AVIRULENT STRAIN OF PSEUDOMONAS-SOLANACEARUM M4S AND ITS BACTERIOPHAGE. TANAKA, H., NEGISHI, H., MAEDA, H. (1990). *Annals of the Phytopathological Society of Japan* 56:243-246.** [TOP OF PAGE]

93. **Bacteriophages and their therapeutic-prophylactic use. Chernomordick, A.B. (1989). *Med. Sestra.* 6:44-47.** [TOP OF PAGE]

94. **[Phagotherapy of postoperative suppurative-inflammatory complications in patients with neoplasms]. [Russian]. Kochetkova, V.A., Mamontov, A.S., Moskovtseva, R.L., Erastova, E.I., Trofimov, E.I., Popov, M.I., Dzhubalieva, S.K. (1989). *Sovetskaia Meditsina* 23-26.** The authors assess the efficacy of phage therapy ofsuppurative and inflammatory complications in oncological patients. A clinical and laboratory analysis has involved 131 patients whose etiotropic therapy consisted of bacteriophages (65 patients) and antibiotics (66). Medicinal phages, manufactured by the Tbilisi Research Institute for Vaccines and Sera, have been administered according to 3 schemes: (1) parallel with antibiotics, (2) after long ineffective antibiotic therapy, (3) phages alone starting from the onset of the purulent complication. The preparations have been prescribed with due consideration for the isolated microflora sensitivity. Incorporation of phages in combined therapy of infectious complications has yielded positive results in 81.5%

of cases, whereas antibiotics have proved effective in but 60.6%. The efficacy of phage therapy depends on the type of pyoinflammatory complications (the results are the best in the management of wound infections), the microflora pattern of the purulent foci (phages are the most effective with a corresponding monoinfection), characteristics of the therapeutic phages proper (Pseudomonas aeruginosa phage is characterized by the highest therapeutic activity, as compared to staphylococcal and other phages). [TOP OF PAGE]

95. **Control of microbiofouling using bacteriophage 2. Detection of phages and fundamental study of their lytic effect on fouling bacteria. Sakaguchi, I., Shinshima, K., Kawaratani, K., Sugai, O. (1989).** ***Denryoku Chuo Kenkyusho Hokoku*** **1-32.** Microbiofouling of condenser tubes of thermal power plants markedly reduces cooling efficiency. Recently a method for controlling microbiofouling using bacteriophages has been receiving consideration. In this paper, studies of the ecological relationship between fouling bacteria and phages, and the lytic activity of phages to fouling bacteria are reported. With thirty cultures of the isolated fouling bacteria from microbial film on glass substratum immersed in flowing seawater at Sendai Bay in north Japan, we carried out the detection and isolation of phages lysing the bacteria from seawater from October 1987 to December 1988 about once per month. The results obtained were as follows: Seventeen cultures were sensitive to phages and were found to belong to *Pseudomonas* (12 strains), *Acinetobacter - Achromobacter* (3 strains), *Vibrio* (1 strain) and *Flavobacterium* (1 strain). Eighteen strains of phages were isolated. A high frequency of phage incidence was observed with the cultures of rapid growing bacteria. But, for cultures of slow growing bacteria, phages were rarely isolated. Under different M.O.I.(multiplicity of infection), the lytic activity of phage to host bacteria was studied. At M.O.I. higher than 0.1, the phage could effectively lyse host bacteria after 5-7 hr of infection. At M.O.I. lower than 0.01, the low level of bacteria concentration was maintained with only slight increase until 48 hr after infection. Various filamentous bacteria were commonly found as predominant species in condenser tube microbiofouling communities.

However we were unable to grow the filamentous bacteria in the standard culture medium used in these experiments. Development of culture methods is necessary in order to develop control methods for filamentous bacteria. [TOP OF PAGE]

96. **IMPROVEMENT OF THE BIOCONTROL OF PSEUDOMONAS-TOLAASII USING BACTERIOPHAGES ASSOCIATED WITH AN ANTAGONISTIC BACTERIUM. GUILLAUMES, J., HOUDEAU, G., GERMAIN, R., Olivier, J.M. (1988).** ***Bulletin OEPP*** **18:77-82.** Improvement of the biocontrol of Pseudomonas tolaasii using bacteriophages associated with an antagonistic bacterium.No chemical control of mushroom bacterial blotch, due to Pseudomonas tolaasii, is available today. Biocontrol using an antagonistic strain of Pseudomonas fluorescens decreases losses with an efficiency of 30-60%, but this is insufficient in practice and so an improvement of the method is required. Among different possibilities, we have studied the use of lytic bacteriophages. Several phages were purified from diseased mushroom caps. Their selectivity was tested using many saprophytic and pathogenic bacteria isolated from different ecosystems. We selected phages strongly aggressive in P. tolaasii and only moderately so in the P. fluorescens strain used for biocontrol. In this way it should be possible to build up a strategy for protecting the casing soil by spraying a mixture of antagonistic bacteria and phages. The first experiments showed that the effects of the antagonistic bacteria and of the phages were additive. The decrease in symptoms was highly significant (> 80%). However, several points have to be resolved before application on a larger scale can be envisaged. Questions also arise on the effect of bacteriophages on the natural population dynamics of Pseudomonas spp. useful or pathogenic to mushrooms. [TOP OF PAGE]

97. **The efficacy of phages in the prevention of the destruction of pig skin in vitro by** ***Pseudomonas aeruginosa*****. Soothill, J.S., Lawrence, J.C., Ayliffe, G.A.J. (1988).** ***Med. Sci. Res.*** **16:1287-1288.** [TOP OF PAGE]

98. **Bacteriophage treatment of suppurative skin infections. Cislo, M., Dabrowski, M., Weber-Dabrowska, B., Woyton, A. (1987).** ***Archivum Immunologii et Therapiae Experimentalis*** **35:175-183.** The study material comprised 31 patients with chronic suppurative infections of the skin caused by Pseudomonas, Staphylococcus, Klebsiella, Proteus and Escherichia. Within 2-16 weeks of the treatment, an improvement of the general state was observed as well as suppression of the local inflammation, purification of a wound from the suppurative and necrotic content, faster healing of the ulcers and fully negative results of the bacteriologic tests. In 16 cases, an outstanding therapeutic effect was obtained, in 7 cases marked improvement was reported and in 2 a transitory improvement was reported. In 7 patients the treatment was abandoned due to the lack of improvement (1 case) or development of side effects (6 cases). The results obtained provide evidence for the high effectiveness of phage therapy in the treatment of suppurative skin infections. [TOP OF PAGE]

99. **Bacteriophage therapy. Dixon, B. (1987).** ***British Medical Journal Clinical Research Ed*** **. 294:1168** [TOP OF PAGE]

100. **Immunogenic effect of bacteriophage in patients subjected to phage therapy. Kucharewicz-Krukowska, A., Slopek, S. (1987).** ***Archivum Immunologii et Therapiae Experimentalis*** **35:553-561.** Fifty seven cases of bacterial infections subjected to phage therapy were tested for a production of antibodies against the applied bacteriophages. Monoinfections confirmed in 40 patients were caused in majority of cases by pyogenic Staphylococci (29 cases) and rarely by Gram-negative bacteria: Klebsiella, Escherichia, Proteus and Pseudomonas (11 cases). Polyinfections caused by the above types of bacteria were recorded in 17 cases. The titer of neutralizing and hemagglutinating antibodies was determined before phage therapy, in the 10th day and in some cases in the 21st day of its course. The effect of natural and immune antibodies on the final result of therapy was analyzed. [TOP OF PAGE]

101. **Results of bacteriophage treatment of suppurative bacterial**

infections in the years 1981-1986. Slopek, S., Weber-Dabrowska, B., Dabrowski, M., Kucharewicz-Krukowska, A. (1987). *Arch. Immunol. Ther. Exp.* 35:569-583. In the years 1981-1986 bacteriophage therapy was applied in 550 cases (100 treated in 1986) of suppurative bacterial infections. Positive results were obtained in 508 cases (92.4%). In 38 cases (6.9%) a transient improvement was observed and in 4 cases (0.7%) phage treatment proved ineffective. Considering that majority of patients (518 cases, 94.2%) were resistant to antibiotic treatment, the results of phage therapy may be regarded as favorable. [TOP OF PAGE]

102. **The control of experimental *Escherichia coli* diarrhoea in calves by means of bacteriophages. Smith, H.W., Huggins, M.B., Shaw, K.M. (1987). *J. Gen. Microbiol.* 133:1111-1126.** [TOP OF PAGE]

103. **Effects of bacteriophage on colonization of sugar beet roots by fluorescent *Pseudomonas* spp. Stephens, P.M., O'Sullivan, M., O'Gara, F. (1987). *Appl. Environ. Microbiol.* 53:1164-1167.** [TOP OF PAGE]

104. **Studies on bacteriophage penetration in patients subjected to phage therapy. Weber-Dabrowska, B., Dabrowski, M., Slopek, S. (1987). *Archivum Immunologii et Therapiae Experimentalis* 35:563-568.** Two healthy volunteers and 56 patients with suppurative bacterial infections were tested for penetration of oral administered bacteriophage to the blood circulation system and urinary tract. In the blood and urine samples collected from patients before phage therapy application, no presence of "wild phages" was confirmed. Examination performed on the 10th day of phage therapy revealed the presence of bacteriophages in 47 of 56 blood samples tested; positive result of examination was obtained in 9 cases of 26 urine samples. [TOP OF PAGE]

105. **The epizootic of milkfish vibriosis and its biological control by bacteriophage AS10. Wu, J.L., Chao, W.J. (1987). In Kou, K.S., Wu, J.L., Hsu, Y.L., Chen, S.N., Tung, M.C., Liao, I.C., and**

Chung, H.Y. (eds.), *THE MEMOIR OF VIROLOGY AND PHARMACOLOGY IN FISH DISEASE. 3.* Taipei. The bacteriophage which infect and lyse Vibrio anguillarum , the pathogen of milkfish vibriosis, was isolated from the overwintering ponds and was named AS10. AS10 had wide spectrum of host range by showing 100% of the virulence in 18 strains of V. anguillarum isolated from the Taiwan area. The optimal stable salinity range of AS10 is 15-45%. By exposing to ultraviolet irradiation, the loss of AS10 infectivity is linearly correlated with U.V. fluence. The pathogenicity of V. anguillarum was almost completely eliminated after 4 h. by AS10 infection at an M. O. I.-1. In the field trial, it is proved that the vibriosis can be inhibited by AS10 application in milkfish overwintering ponds. [TOP OF PAGE]

106. **Predatory Myxobacteria: Lytic Mechanisms and Prospects as Biological Control Agents for Cyanobacteria (Blue-Green Algae). Lake Restoration: Protection and Mangement. Burnham, J.C., Fraleigh, P. (1986).** ***U.S.EPA Symposium Volume*** **EP-A4401/583001, 249-256.** [TOP OF PAGE]

107. **Homologous bacteriophage control of *Pseudomonas* growth and beef spoilage. Greer, G.G. (1986).** ***J. Food Prot.*** **49:104-109.** [TOP OF PAGE]

108. **Bacteriophage control of beef spoilage. Greer, G.G. (1986).** ***J. Food Prot.*** **49:104-???** [TOP OF PAGE]

109. **Efficiency of preventive treatment by phage preparations of children's hospital salmonellosis. Kilnadze, G.P., Gadua, M.M., Tsereteli, E.V., Mchedlidze, L.S., Birkadze, T.V. (1986).** pp. **41-44.** In In **Kiknadze, G.P.** (ed.), ***Intestinal Infections.*** **Sovetskaya Meditsina, Tbilisis, Georgia.** [TOP OF PAGE]

110. **Constraints on the coevolution of bacteria and virulent phage: A model, some experiments, and predictions for natural communities. Lenski, R.E., Levin, B.R. (1985).** ***Am. Nat.*** **125:585-602.** One view

of the coevolution of parasites and their hosts is that of a gene-for-gene arms race between host defenses and parasite counterdefences. We have incorporated mutations into a model of the ecological interactions between bacteria and virulent phage to determine rates of mutation that would be consistent with this scenario. The model assumes an open habitat (e.g., a chemostat) in which virulent phage and sensitive bacteria can coexist. Equilibrium densities of bacteria and phage are inversely proportional to the efficiency with which phage irreversibly adsorb to their hosts. The absolute rate at which mutations appear is proportional to the product of habitat size, population density, rate of increase, and mutation rate. ¶ The bacterium *Escherichia coli* B readily evolved resistance to virulent phage T4 in our chemostat experiments. Approximately 100 h was required for the appearance, establishment, and attainment of a resourse-limited population of these T4-resistant mutants; this time period is close to that predicted from the model when the parameters of the model are estimated independently. No hostrange phage T4 mutants appeared, yet the phage persisted even after the resistant bacteria had become resource-limited. We hypothesized that the failure to observe corresponding phage mutants indicates mutational constraints on the coevolutionary potential of this phage. We also hypothesized that the persistence of the wild-type phage indicates the presence of a minority population of sensitive bacteria that persists because of selective constraints which produce a competitive disadvantage for resistant baceria under resource-limiting conditions. Both of these hypotheses were verified. Host-range T4 mutants occurred at a rate on the order of 10^{-12} or less, and could not be expected in the chemostats for several years. T4-sensitive and -resistant bacteria had very nearly the same exponential growth rates, but at steady state the latter had approximately a 50% disadvantage. ¶ We also examined the interactions of *E. coli* B and virulent phages T2, T5, and T7 for evidence of selective and mutational constraints on the bacteria and phage, respectively. Under the conditions of our experiments, T2-resistant and T7-resistant (but not T4-resistant) bacteria also had clear competitive disadvantages to sensitive bacteria udner resource-limiting conditions. We were able to

isolate T2 and T7 (but not T5) host-range mutants. Even with T2 and T7, however, we could not select indefinitely for host-range mutants active against higher-order resistant bacteria. This general asymmetry in the coevolutionary potential of bacteria and phage occurs becuase mutations conferring resistance may arise by either the loss or alteration of gene function, while host-range mutations depend on specific alterations of gene function. ¶ These constraints preclude observing endless arms races between baceria and virulent phage. Instead, because of the asymmetry in coevolutionary potential of these hosts and parasites, we anticipated that natural communities of coliform bacteria and virulent coliphage are dominated by bacterial clones resistant to all co-occurring virulent phage. If virulent pahge to which the dominant clones are sensitive should appear, then bacteria will either rapidly evolve resistance or be replaced by existing clones resistant to the phage. Thus, the role of virulent phage in structuring communities of bacteria is seen as important in determining clonal composition but uninportant in determining bacterial densities. [TOP OF PAGE]

111. **Bacteria and phage: A model system for the study of the ecology and co-evolution of hosts and parasites. Levin, B.R., Lenski, R.E. (1985).** pp. 227-242. In In **Rollinson, D. and Anderson, R.M.** (eds.), ***Ecology and Genetics of Host-Parasite Interactions.*** **Academic Press, London.** The results are reviewed of theoretical and experimental investigations of the population biology of bacteria and bacteriophage, emphasizing those apsects of general interest in the study of host-parasite ecology and evolution. ¶ 1) *Existence conditions:* the conditions are considered udner which phage can invade bacterial populations and will stably co-exist with these hosts. Particular emphasis is given to the effects of phage resistant bacterial clones on these communities, and hypotheses are presented to account for the observation that experimental populations of bacteria and virulent phage are more stable than anticipated from theory. ¶ 2) *Co-evolution:* The nature and effects of selection on the interacting populations of bacteria and phage are examined. Evidence is presented that the resulting co-evolution is a constrained process, rather than the

indefinite gene-for-gene arms race previously postulated. ¶ 3) *Latency:* Temperate bacteriophage are analogous to the latent virusses of eukaryotes. We critically discuss three classes of hypotheses for the ecological conditions and selective pressures responsible for the evolution and maintenance of temperate (as opposed to virulent) modes of phage reproduction. ¶ 4) *Immunity:* Bacterial restriction-modification systems are similar to the immune systems of higher organisms. The hypothesis is considered that restriction-modification systems evolved nad are maintained for the defence against phage infection and we speculate on the effects of this type of immune system on the population dynamics of bacteria and phage. ¶ 5) *Coda:* This review is concluded with a brief consideration of the use of phage for the biological control of bacteria. [TOP OF PAGE]

112. **LARGE-SCALE PRODUCTION OF PRUNIPHAGE FOR BIOCONTROL OF PRUNUS BACTERIAL SPOT DISEASE IN FIELD. RANDHAWA, P.S., Civerolo, E.L. (1985).** ***Phytopathology*** **75:1328** [TOP OF PAGE]

113. **Results of bacteriophage treatment of suppurative bacterial infections. V. Evaluation of the results obtained in children. Slopek, S., Kucharewicz-Krukowska, A., Weber-Dabrowska, B., Dabrowski, M. (1985).** ***Archivum Immunologii et Therapiae Experimentalis*** **33:241-259**. The results of phage therapy applied in 114 cases of suppurative bacterial infections in children were analyzed. Positive therapeutic results were obtained in 109 (95.6%) cases. The results confirmed great effectiveness of bacteriophages in the treatment of septic infections, spontaneous or postoperative, caused by pyogenic Staphylococci, Klebsiella, Escherichia, Proteus and Pseudomonas bacteria. [TOP OF PAGE]

114. **Results of bacteriophage treatment of suppurative bacterial infections. IV. Evaluation of results obtained in 370 cases. Slopek, S., Kucharewicz-Krukowska, A., Weber-Dabrowska, B., Dabrowski, M. (1985).** ***Arch. Immunol. Ther. Exp.*** **33:219-???** [TOP OF PAGE]

115. **Results of bacteriophage treatment of suppurative bacterial infections. VI. Analysis of treatment of suppurative staphylococcal infections. Slopek, S., Kucharewicz-Krukowska, A., Weber-Dabrowska, B., Dabrowski, M. (1985).** ***Archivum Immunologii et Therapiae Experimentalis*** **33:261-273.** Analysis of phage therapy results was carried out on 273 cases of spontaneous and postoperative septic staphylococcal infections. The treatment appeared effective in 254 (93.0%) cases. Detailed analysis of the results obtained in particular disease categories revealed that staphylococcal bacteriophages may be efficiently applied in the treatment of suppurative staphylococcal infections resistant to antibiotics. [TOP OF PAGE]

116. **[Experience with bacteriophage therapy in nonspecific suppurative lung diseases]. [Russian]. Timoshchuk, I.I., Natsiashvili, E.I., Chanishvili, T.G., Meladze, G.D. (1985).** ***Grudnaia Khirurgiia*** **11-13.** [TOP OF PAGE]

117. **Preventive effectiveness of dried polyvalent *Shigella* bacteriophage in organized collective groups. Anpilov, L.I., Prokudin, A.A. (1984).** ***Voenno-Med. Zh.*** **5:39-40.** [TOP OF PAGE]

118. **Attack of the phages. Dixon, B. (1984).** ***Science 84*** **, 66-69.** [TOP OF PAGE]

119. **The use of a lytic bacteriophage to remove *Rhizobium trifolii* from protoplast culture of *Trifolium repens*. Graves, D.A., Beck, R.W. (1984).** ***Plant Sci. Lett.*** **34:385-???** [TOP OF PAGE]

120. **Psychrotropic bacteriophages for beef spoilage bacteria. Greer, G.G. (1984).** ***J. Food Prot.*** **47:822** [TOP OF PAGE]

121. **Mucoid conversion by phages of *Pseudomonas aeruginosa* strains from patients with cystic fibrosis. Miller, R.V., Renta Rubero, J.R. (1984).** ***J. Clin. Microbiol.*** **19:717-???** [TOP OF PAGE]

122. **[Bacteriophages and phage therapy in pediatric practice]. [Review] [21 refs] [Russian]. Samsygina, G.A., Boni, E.G. (1984).** ***Pediatriia*** **67-70.** [TOP OF PAGE]

123. **Results of bacteriophage treatment of suppurative bacterial infections. III. Detailed evaluation of the results obtained in further 150 cases. Slopek, S., Durlakowa, I., Weber-Dabrowska, B., Dabrowski, M., Kucharewicz-Krukowska, A. (1984).** ***Archivum Immunologii et Therapiae Experimentalis*** **32:317-335.** The results of phage therapy applied in further 150 cases of suppurative bacterial infections were analyzed. Positive therapeutic results were obtained in 137 cases (91.3%). The results obtained confirmed the previous findings on great effectiveness of bacteriophages in the treatment of septic infections, spontaneous or postoperative, caused by pyo genic Staphylococci, Klebsiella, Escherichia, Proteus and Pseudomonas. [TOP OF PAGE]

124. **Phage therapy. Anonymous (1983).** ***Lancet*** **2(8362):1287-1288.** [TOP OF PAGE]

125. ***Viral Control of Nuisance Cyanobacteria (Blue-Green Algae). II. Cyanophage Strains, Stability on Phages and Hosts, and Effects of Environmental Factors on Phage-Host Interactions.*** **Desjardins, P.R., Olson, G.B. (1983). California Water Resourse Center, University of California, Davis, CA.**[TOP OF PAGE]

126. **Cyanophage: Histroy and likelihood as a control. Desjardins, P.R. (1983).** p. **242-???** Anonymous***Lake Restoration, Protection, and Management.*** **Environmental Protection Agency, Washington, D.C.** [TOP OF PAGE]

127. **Use of UV-irradiated bacteriophage T6 to kill extracellular bacteria in tissue culture infectivity assays. Shaw, D.R., Maurelli, A.T., Goguen, J.D., Straley, S.C., Curtiss, R.I. (1983).** ***J. Immunol. Methods*** **56:75-83.** We have utilized 'lysis from without' mediated by

UV-inactivated bacteriophage T6 to eliminate extracellular bacteria in experiments measuring the internalization, intracellular survival and replication of Yersinia pestis within mouse peritoneal macrophages and of Shigella flexneri within a human intestinal epithelial cell line. The technique we describe has the following characteristics: (a) bacterial killing is complete within 15 min at 37 degrees C, with a greater than 10(3)-fold reduction in colony-forming units (CFU); (b) bacteria within cultured mammalian cells are protected from killing by UV-inactivated T6; (c) the mammalian cells are not observably affected by exposure to UV-inactivated T6. This technique has several advantages over the use of antibiotics to eliminate extracellular bacteria and is potentially widely applicable in studies of the interactions between pathogenic bacteria and host phagocytic cells as well as other target tissues. [TOP OF PAGE]

128. **Results of bacteriophage treatment of suppurative bacterial infections. I. General evaluation of the results. Slopek, S., Durlakova, I., Weber-Dabrowska, B., Kucharewicz-Krukowska, A., Dabrowski, M., Bisikiewicz, R. (1983).** ***Arch. Immunol. Ther. Exp.*** **31:267-???** [TOP OF PAGE]

129. **Results of bacteriophage treatment of suppurative bacterial infections. II. Detailed evalulation of the results. Slopek, S., Durlakova, I., Weber-Dabrowska, B., Kucharewicz-Krukowska, A., Dabrowski, M., Bisikiewicz, R. (1983).** ***Arch. Immunol. Ther. Exp.*** **31:293-???** [TOP OF PAGE]

130. **Effectiveness of phages in treating experimental Escherichia coli diarrhoea in calves, piglets and lambs. Smith, H.W., Huggins, M.B. (1983).** ***J. Gen. Microbiol.*** **129:2659-2675.** [TOP OF PAGE]

131. **Psychotrophic bacteriophages for beef spoilage pseudomonads. Greer, G.G. (1982).** ***J. Food Prot.*** **45:1318-1325.** [TOP OF PAGE]

132. **Teh efficacy of staphylococcal bacteriophage in treatment of purulent diseases of lungs and pleura. Meladze, G.D., Mebuke, M.G.,**

Chkhetia, N.S., Kiknadze, N.I., Koguashvili, G.G., Timoshuk, I.I., Larionova, N.G., Vasadze, G.K. (1982). *Grudnaia Khirurgiia* 1:53-56. [TOP OF PAGE]

133. **Successful treatment of experimental *Escherichia coli* infections in mice using phage: Its general superiority over antibiotics. Smith, H.W., Huggins, M.B. (1982). *J. Gen. Microbiol.* 128:307-318.** [TOP OF PAGE]

134. **STUDIES ON A BACTERIO PHAGE ISOLATED FROM XANTHOMONAS-CAMPESTRIS 2. ITS USE IN THE CONTROL OF XANTHOMONAS-CAMPESTRIS AND XANTHOMONAS-CAMPESTRIS-VESICATORIA. BERGAMIN, F.I.L.H., KIMATI, H. (1981). *Summa Phytopathologica* 7:35-43.** Studies on a bacteriophage isolated from Xanthomonas campestris: 2. Its use in the control of Xanthomonas campestris and Xanthomonas campestris vesicatoria.The phage described can be used successfully, at least under greenhouse conditions, in the control of the cabbage disease caused by X. campestris and the pepper disease caused by X. vesicatoria. For both diseases the most efficient treatment was simultaneous inoculation with the phage and bacteria. The symptoms were reduced in 99.83% for X. campestris and 99.02% for X. vesicatoria. [TOP OF PAGE]

135. **Experience in the therapeutic use of bacteriophage preparations in suppurative surgical infections. Peremitina, L.D., Berillo, E.A., Khvoles, A.G. (1981). *Zh. Mikrobiol. Epidemiol. Immunobiol.* 9:109-110.** [TOP OF PAGE]

136. **Therapy of experimental tuberculosis in guinea pigs with mycobacterial phages DS-6A, GR-21 T, My-327. Sula, L., Sulova, J., Stolcpartova, M. (1981). *Czechoslovak Medicine* 4:209-214.** Guinea pigs, weighing 250-350 g, were infected with approximately 5,000 of live germs M- tuberculosis H 37 Rv grown 10 days in deep culture of liquid semisynthetic medium according to Sula. The infection was performed subcutaneously in inquinal region. For the therapy

following phages were used: DS-6A, GR-21/T, My-327 injected twice a week subcutaneously in the dose of 10(6)/1 ml of live particles for 10 weeks. The therapeutic effect was expressed by spleen and hilus index. Out of the phages used, phage DS-6A had the highest therapeutic effect with mean spleen index of 0.19, corresponding approximately to the spleen index reached with the most effective tuberculostaticum INH. The exact explanation of the phage therapeutic effect in given experimental conditions, when the phages are not applied locally in order to gain the direct contact with infectious antigens, is not known. It is suggested that there presumably exists an interaction between the released phage nucleic acid and the nucleic acid synthesis needed for the growth of mycobacteria in vivo. [TOP OF PAGE]

137. **Korrektsiia disbakterioza kishechnika biologicheskimi preparatami u bol'nykh ostrymi leiozami. [Correction of intestinal dysbacteriosis with biological preparations in acute leukemia]. Tolkachera, T.Y., Abakumova, E.M., Martynova, V.A., Golosova, T.V. (1981).** ***Problemy Germatologii i Perelivaniia Krovi*** **26:29-33.** [TOP OF PAGE]

138. **Biological Control of Fish Bacterial Pathogen, Aeromonas hydrophila by Bacteriophage AH 1. Wu, J.L., Lin, H.M., Jan, L., Hsu, Y.L., Chang, L.H. (1981).** ***Fish Pathol.*** **15:271-276.** The usefulness of the bacteriophages as a biological control agent for cultured fish diseases is discussed. The authors have initiated the isolation of bacteriophages to infect Aeromonas hydrophila which is the pathogen of eel's red-fin disease. Among the eight isolated bacteriophages, AH1 has strongest bacteria-lysis ability. Therefore, AH1 was selected as the experimental model system for the study of biological control of diseases. The one-step growth curve showed that AH1 started to form phage particles after 50 min of infection and completed at 100 min with a burst size of 160. One AH1-infected A. hydrophila can produce 160 phage particles. In order to test the loss of pathogenecity of A. hydrophila after AH1 infection, the AH1-infected bacteria were injected to loach Misgurnus anguillicaudatus . After 3 infection of AH1, the A. hydrophila had completely lost its infectivity and mortality in the injected loaches. [TOP

OF PAGE]

139. **Investigation of the effect of Brucella-phage on the course of experimental infection with *Brucella abortus*. Corbel, M.J., Morris, J.A. (1980). *Br. Vet. J.* 136:278-???** [TOP OF PAGE]

140. **Ecology of Streptococcus faecium bacteriophage in chicken gut. Houghton, S.B., Fuller, R. (1980). *Appl. Environ. Microbiol.* 39:1054-1058.** The interaction in the chick gut between Streptococcus faecium and its phage was examined. In conventional chicks, large numbers of S. faecium and phage were found in the cecum and smaller numbers were found in the anterior gut. In gnotobiotic chicks associated with S. faecium SY1 and its phage, there was no marked effect on bacterial numbers, but resistance to the phage rapidly developed. Depression of chick growth caused by S. faecium strain SY1 was partially reversed by its phage. [TOP OF PAGE]

141. **Use of bacteriophages and antibiotics for prevention of acute postoperative empyema in chronic suppurative lung diseases. Ioseliani, G.D., Meladze, G.D., Chkhetiia, N.S., Mebuke, M.G., Kiknadze, N.I. (1980). *Grudnaia Khirurgiia* 6:63-67.** [TOP OF PAGE]

142. **Effect of a bacteriophage on the colonization and nodulation of clover roots by a strain of *Rhizobium trifollii*. Evans, J., Barnet, Y.M., Vincent, J.M. (1979). *Can. J. Microbiol.* 25:968-973.** [TOP OF PAGE]

143. **Bacteriophage therapy of septic complications of orthopaedic surgery. Lang, G.P., Kehr, P., Mathevon, H., Clavert, J.M., Sejourne, P., Pointu, J. (1979). *Rev. Chir. Orthop. Reparatrice Appar. Mot.* 1:33-37.** [TOP OF PAGE]

144. **Evaluation of efficacy of the use of *E. coli-Proteus* bacteriophage in intestinal dysbacteriosis in premature infants. Litvinova, A.M., Chtetsova, V.M., Kavtreva, I.G. (1979). *Vopr. Okhr. Materin. Det.***

9:42-44. [TOP OF PAGE]

145. **Données actuelles sur les applications thérapeutiques des bactériophages. Vieu, J.-F., Guillermet, F., Minck, R., Nicolle, P. (1979). *Bull. Acad. Natl. Med.* 163:61-???** [TOP OF PAGE]

146. **Traitement d'une endocardite à *Serratia* par les bactériophages. Grimont, P.-A.D., Grimont, F., Lacut, J.-Y., Issanchou, A.-M., Aubertin, J. (1978). *Nouv. Presse Med.* 7:2251-???** [TOP OF PAGE]

147. **Decontamination of bacterial infection of monolayer cultures with a specific bacteriophage. Riche, P.H., Vic, P., Humeau, C., Vanneraeau, H., Vlahovitch, B., Sentein, P. (1978). *In Vitro* 14:935-???** [TOP OF PAGE]

148. **Succession of *Streptococcus bovis* strains with differing bacteriophage sensitivities in the rumens of two fistulated sheep. Iverson, W.G., Millis, N.F. (1977). *Appl. Environ. Microbiol.* 33:810-813.** The bacteriophage sensitivity of the *Streptococcus bovis* population resident in the ruments of two fistulated sheep was monitored for 112 days. During this time, three changes in the bacteriophage sensivity of *S. bovis* occurred in the absence of detectable bacteriophages. Identical changes in bacteriophage sensitivity occurred simultaneously in both animals and, except for the relatively short periods of changeover in phage sensitivity, the *S. bovis* population in the rumens of the two sheep was homogeneous with respect to phage sensitivity. [TOP OF PAGE]

149. **Recovery and susceptibility pattern of faecal streptococci bacteriophages. Saleh, F.A. (1977). *Water Res.* 11:403-409.** [TOP OF PAGE]

150. **[Experience with treating complicated forms of abscessing pneumonia in children]. [Russian]. Pipiia, V.I., Eteriia, G.P., Gotua, T.P., Volobuev, V.I., Katsarava, V.S. (1976). *Vestnik Khirurgii Imeni i - i***

- *Grekova* **117:64-68**. Under observation were 157 patients with different forms of abscessing pneumonias. Pleural complicaitons were noted in 113 patients (about 60%). The complex treatment was employed in all patients (intensive antibacterial therapy, immunotherapy, bacteriophage, administration of protein preparations, vitamin-therapy, fresh blood transfusion, artery system and by means of percutaneous catheterization of th subclavian vein. The results of the treatment are described. [TOP OF PAGE]

151. **Prospects for control of phytopathogenic bacteria by bacteriophage and bacteriocins. Vidaver, A.K. (1976).** ***Ann. Rev. Phytopathol.*** **14:451-???** [TOP OF PAGE]

152. ***Topley and Wilson's Principles of Bacteriology and Immunity.*** **Wilson, G.S., Miles, A.A. (1975). p.1634-1636. Edward Arnold, London.**[TOP OF PAGE]

153. **The occurrence of bacteriophages in the rumen and their influence on rumen bacterial population. Orpin, C.G., Munn, E.A. (1974).** ***Experimentia*** **30:1018-1020.** [TOP OF PAGE]

154. **Use of combined phages in suppurative-inflammatory diseases. Sakandelidze, V.M., Meipariani, A.N. (1974).** ***Zh. Mikrobiol. Epidemiol. Immunobiol.*** **6:135-136.** [TOP OF PAGE]

155. **[Materials on the study of bacteriophage therapy of deep forms of staphyloderma]. [Russian]. Vartapetov, A.I. (1974).** ***Vestnik Dermatologii i Venerologii*** **8-11.** [TOP OF PAGE]

156. **The fate of bacteriophage lambda in non-immune germ-free mice. Geier, M.R., Trigg, M.E., Merril, C.R. (1973).** ***Nature*** **246:221-223.** [this is cited in Merril et al., 1996 (PNAS 93:3188-3192): ". . . even in the absence of an antibody response, bacteriophage tend to be rapidly eliminated from the circulation by the reticuloendothelium system (ref)"]. [TOP OF PAGE]

157. Failure to produce experimental sarcoidosis in guinea pigs with *Mycobacterium tuberculosis* and mycobacteriophage DS6A. Boman, B.U., Amos, W.T., Geer, J.C. (1972). *Am. Rev. Respir. Dis.* 105:85-94. [TOP OF PAGE]

158. Biological agents which cause lysis of blue-green algae. Shilo, M. (1971). *Vehr. Int. Verein. Limnol.* 19:206-213. [TOP OF PAGE]

159. Algal viruses-eutrophication control potential. Jackson, D., Sladecek, V. (1970). *Yale Sci.* 44:16-21. [TOP OF PAGE]

160. Use of staphylococcal bacteriophage for therapeutic and preventive purposes. Proskurov, V.A. (1970). *Zh. Mikrobiol. Epidemiol. Immunobiol.* 2:104-107. [TOP OF PAGE]

161. Phage treatment for severe burns. Shera, G. (1970). *Br. Med.* 1:568-??? [TOP OF PAGE]

162. A study of the therapeutic effect of bacteriophage agents in a complex treatment of suppurative surgical diseases. Zhukov-Verezhnikov, N.N., Peremitina, L.D., Berillo, E.A., Komissarov, V.P., Bardymov, V.M., Khvoles, A.G., Ugryumov, L.B. (1970). *Sov. Med.* 12:64-66. [TOP OF PAGE]

163. Inhibition of bacterial spot of peach foliage by *Xanthomonas pruni* bacteriophage. Civerolo, E.L., Kiel, H.L. (1969). *Phytopathology* 59:1966-1977. [TOP OF PAGE]

164. Bacteriophages of psychophilic pseudomonads. I. Host range of phage pools active against fish spoilage and fish-pathogenic pseudomonads. Delisle, A.L., Levin, R.E. (1969). *Antonie van Leeuwenhoek J. Microbiol.* 35:307-317. [TOP OF PAGE]

165. Die bakteriophagie in der Therapie und Prophylaxe der

Infektionskranheiten. Mazácek, M., Petera, A., Mach, J. (1969). *Zentralbl. Bakteriol. Parasienkd. Infektionskr. Hyg. Abt. 1 Orig. Reihe A* 211:385-??? [TOP OF PAGE]

166. Felix d'Herelle and bacteriophage therapy. Peitzman, S.J. (1969). *Transactions and Studies of the College of Physicians of Philadelphia* 37:115-123. [TOP OF PAGE]

167. [Assumptions for successful therapy using staphylococcal phage lysates]. [German]. Pillich, J., Vymola, F., Buda, J. (1969). *Zentralblatt Fur Bakteriologie, Parasitenkunde, Infektionskrankheiten Und Hygiene - 1 - Abt - Medizinisch-Hygienische Bakteriologie, Virusforschung Und Parasitologie - Originale* 210:377-381. [TOP OF PAGE]

168. [Further data on the association of bacteriophage with antibiotic therapy for the purpose of sterilizing carriers of dysentery bacilli]. [French]. Zilisteanu, C., Mintzer-Morgenstern, L., Ionesco, H., Ionesco-Dorohoi, T. (1969). *Archives Roumaines de Pathologie Experimentales et de Microbiologie* 28:1073-1080. [TOP OF PAGE]

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171. [Effectiveness of phage therapy in experimental proteus infection]. [Russian]. Matusis, Z.E., Mel'nikov, V.D., Gerasimov, A. (1967). *Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii* 44:100-103.

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172. [Lytic activity of the bacteriophage used in planned phage therapy in children's institutions in Perm in 1963-1965]. [Russian]. Smirnova, N.P. (1967). *Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii* 44:136-137. [TOP OF PAGE]

173. Bacteriophage therapy in infective childhood asthma. Wittig, H.J., Raffetto, J.F., Bason, R. (1966). *J. Am. Med. Assoc.* 196:435 [TOP OF PAGE]

174. Discussion on the bacteriophage (bacteriolysin). d'Herelle, F., Twort, F.W., Bordet, J., Gratia, A. (1965). p. ???-??? In Stent, G. (ed.), *Papers on Bacterial Viruses*. Little, Brown and Co., Boston. [TOP OF PAGE]

175. [Association of bacteriophage with antibiotic therapy for the sterilization of carriers of dysentery bacilli]. [French]. Zilisteanu, C., Filotti, A., Mintzer-Morgenstern, L., Ghyka, G. (1965). *Archives Roumaines de Pathologie Experimentales et de Microbiologie* 24:1021-1028. [TOP OF PAGE]

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179. Treatment and prophylaxis of cholera with bacteriophage. Sayamov, R.M. (1963). *Bull. W. H. O.* 28:361-??? [TOP OF PAGE]

180. ***Molecular Biology of Bacterial Viruses.*** **Stent, G. (1963). WH Freeman and Co., San Francisco, CA.**[TOP OF PAGE]

181. **Die therapeutische Anwendung von Bakteriophagen unter besonderer Berücksichtigung des Typhus and Paratypus B. Clajus, W. (1959).** ***Zentralbl. Bakteriol. Parasitenkd. Infektionskr. Hyg. Atb. 1 Ref.*** **170:427-???** [TOP OF PAGE]

182. ***Cholera.*** **Pollitzer, R. (1959). World Health Organization,** ["The World Health Organization came to the conclusion that, with the success of tetracycline therapy, there did not seem any reason why investigation into phage therapy should continue." --- Quoted from Barrow & Soothill, 1997]. [TOP OF PAGE]

183. **A study of the action of bacteriophage on some diseases of tomato and cabbage. Gutermuth, C. (1958). Kent State University.** [TOP OF PAGE]

184. **Fate of bacteriophage particles induced into mice by various routes. Keller, R., Engley, F.B. (1958).** ***Proc. Soc. Exp. Biol. Med.*** **98:577-???** [TOP OF PAGE]

185. **The acquired resistance of *Staphylococcus aureus* to bacteriophage. Lowbury, E.J.L., Hood, A.M. (1953).** ***J. Gen. Microbiol.*** **9:524-535.** To test the capacity of different staphylococci to acquire resistance to bacteriophage *in vitro*, twenty phages were grown on solid medium and in fluid medium wiht their propagating strains of *Staphylococcus aureus*, different phage types and patterns being represented. ¶ Resistant secondary growth never appeared among staphylococci of the 3A group and often appeared among members of the 6/47 group. Some members of the 29/52 group acquired resistance readily, and others never became resistant. Cross-resistance to other phages was commonly acquired. Secondary growth was shown to be resistant or sensitive to thephage, or to yield a mixture of resistant and sensitive colonies. ¶ With the exception of propagating strain PS 69, all staphylococci which

became resistant to phage acquired lysogenicity for the sensitive parent strain. All but one of the staphylococci which had acquired resistance to a phage appeared to be capable of absorbing that phage. A substance which caused non-specific inhibition of phage lysis on agar medium was present in phage lysates of a staphylococcus that had shown sensitive secondary growth. These results are discussed with reference to phage typing and to the possibilities of therapy by phage. [TOP OF PAGE]

186. ***The Bacteriophage: A Historical and Critical Survey of 25 Years Research.*** **Flu, P.C. (1946). Universitaire Pers Leiden, Leiden.**[TOP OF PAGE]

187. ***Le Bactériophage: Sa Nature et son Emploi Thérapeutique.*** **Steinmann, J. (1946).** [TOP OF PAGE]

188. **Bacteriophage therapy in bacillary dysentery. Boyd, J.S.K., Portnoy, B. (1944).** ***Trans. R. Soc. Trop. Med. Hyg.*** **37:243-262.** ["Some well controlled studies (on bacteriophage therapy), both experimental and clinical, produced results that were negative or where the observed effects were not regarded as useful." Quoted from Barrow & Soothill, 1997]. [TOP OF PAGE]

189. **The multiplication of bacteriophage in vivo and its protective effects against an experimental infection with *Shigella dysenteriae*. Dubos, R.J., Straus, J.H., Pierce, C. (1943).** ***J. Exp. Med.*** **78(20?):161-168.** ["Inocultated mice intracerebrally with 10^6 colony-forming units (cfu) of *Shigella dysenteriae*, which resulted in an acute cerebritis and meningitis followed by death of 8/8 mice within 2-5 days. Simultaneous intraperitoneal inoculation with 10^9 plaque-forming units (pfu) of an unpurified phage suspension produced 6/8 animals, while inoculation with a lower dose (10^5 pfu) protected 2/8 mice. There was evidence that the phages had multiplied *in situ* in the brain and had crossed the blood-brain barrier as a result of the bacterial infection." Quoted from Barrow & Soothill, 1997]. [TOP OF PAGE]

190. **Bacteriophagy in the developing chick embryo. Rakieten, T.L., Rakieten, M.L. (1943). *J. Bacteriol.* 45:477-484.** [TOP OF PAGE]

191. **Protective action of VI bacteriophage in Eberthella typhi infections in mice. Ward, W.E. (1943). *J. Infect. Dis.* 72:172-176.** Mice were infected, by use of he mucin technic, with strains of Eberthella typhi in the Vi phase. Blood stream invasion occurred within an hour following injection. It was possible to protect more than 90% of infected mice when intravenous specific bacteriophage treatment was instituted within 4 hours following infection. Nontreated mice and mice treated with nonspecific bacteriophage showed a mortality approaching 100%. ¶ Titrations on the heart blood from specifically treated animals showed an increase in bacteriophage concentration over a period of several hours with detectable phage present for more than 60 hours. Bacteriophage disappeared in a very few hours from the blood of infected miced treated with bacteriophage not active for the infecting strain. ¶ Treated mice were healthy carriers of the infecting organisms for about one month after infection. However, in many cases these organisms were in the degraded or W form. [TOP OF PAGE]

192. ***Treatment of wounds with bacteriophages*. Pokrovskaya, M.P., Kaganova, L.C., Morosenko, M.A., Bulgakova, A.G., Skatsenko, E.E. (1942). State Publishing House "Medgiv", Moscow, USSR.** [TOP OF PAGE]

193. **Effect of bacteriophage in experimental staphylococcal septicemia in rabbits. Bronfenbrenner, J.J., Sulkin, S.E. (1941). *J. Bacteriol.* 41:61-61.** The present experiments were undertaken to evaluate the validity of the reports of successful bacteriophage therapy in clinical staphylococcal infections. Rabbits were infection by the intravenous introduction of staphylococci of varying degrees of virulence and were submitted to therapy with bacteriophage propagated on each of the respective strains of the organisms. While no definite therapeutic effect was attained in any instance, the use of bacteriophage propagated on the invasive staphylococcus prolonged and increased the

severity of the course of the infection irrespective of the degree of virulence of the infecting organism. [TOP OF PAGE]

194. **Use of bacteriophage for freeing protozoal cultures of contaminating bacteria (isolation of *Leptospira icterohaemorrhagiae* from mixed infections in guinea-pigs). DeMonte, A.J.H., Gupta, S.K. (1941). *Indian Med. Gaz.* 76:154-???** [TOP OF PAGE]

195. **The bacteriophage: Its nature and its therapeutic use (II). Krueger, A.P., Scribner, E.J. (1941). *J. Am. Med. Assoc.* 116:2269-2277.** [TOP OF PAGE]

196. **The bacteriophage: Its nature and its therapeutic use (I). Krueger, A.P., Scribner, E.J. (1941). *J. Am. Med. Assoc.* 116:2160-2167.** [TOP OF PAGE]

197. **Bacteriophage therapy. II. Prophylactic and therapeutic effect of bacteriopahge and of antivirus in experimental infections of the eye. Bronfenbrenner, J.J., Sulkin, E. (1939). *J. Infect. Dis.* 65:58-???** [TOP OF PAGE]

198. **Bacteriophage therapy. III. On the nature of the deleterious effect of the local application of staphylococcus bacteriophage. Bronfenbrenner, J.J., Sulkin, E. (1939). *J. Infect. Dis.* 65:64-???** [TOP OF PAGE]

199. **The inactivation of "pure line" phages by bacterial extracts and the loss of phage types in vivo. Rakieten, M.L., Rakieten, T.L. (1938). *Yale J. Biol. Med.* 10:191-208.** [TOP OF PAGE]

200. **The effect of an anti-Vi bacteriophage on typhoid infection in mice. Asheshov, I.N., Wilson, J., Topley, W.W.C. (1937). *Lancet* 1:319-320.** ["Showed some protection against different bacterial infections in animals given very large doses of phage." Quoted from Barrow & Soothill, 1997]. [TOP OF PAGE]

201. **Bacteriophage and antivirus therapy of localized experimental infections with staphylococcus. Bronfenbrenner, J.J., Sulkin, S.E. (1936). *J. Bacteriol.* 31:56-56.** [TOP OF PAGE]

202. **The bacteriophage in relation to Salmonella pullora infection in the domestic fowl. Pyle, N.J. (1936). *J. Bacteriol.* 12:245-261.** The purpose of this work has been first to study the intestinal contents, fluids and tissues from the domestic fowl, and to locate and identify in these materials a bacteriophage, lytic for *Salmonella pullora* (*Bacterium pullorum* Rettger). ¶ Secondly, methods have been employed for increasing the lytic activity of the avian bacteriophage *in vitro*, to the end of using it as a therapeutic reagent in avian therapeutics. ¶ From the data presented and the observations made, the following conclusions appear to be justified. ¶ 1. Tissues of the domestic fowl do contain bacteriophages causing lysis of various strains of *Salmonella pullora*. ¶ 2. Up to the present time, although these avian "phages" are lytic for *Salmonella pullora*, it has not been demonstrated that they are specific for this organism. ¶ 3. When agar slant cultures of *Salmonella pullora* are treated with liquid cultures of these avian bacteriophages which are lytic for *Salmonella pullora*, watery, moth-eaten or pellucid areas are demonstrated. This fact, together with the demonstration of the transmission of bacteriophagy for *Salmonella pullora* in series would indicate that the transmissible bacteriolysis is a living ultra-microscopic entity. These reactions of the avian bacteriophage are characteristic of d'Herelle's "Bacteriophagum Intestinale." ¶ 4. Although the bacteriophages isolated and studied have demonstrated marked bacteriolysis *in vitro*, the evidence from animal experiments does not indicate that as now prepared and used that they have much therapeutic effect in freeing the bird's body of infection. ¶ 5. Bacteriophages actively bacteriolytic for *Salmonella pullora* have been isolated from domestic fowls showing a high agglutinative titre for this organism. ["Some well controlled studies (on bacteriophage therapy), both experimental and clinical, produced results that were negative or where the observed effects were not regarded as useful." Quoted from Barrow

& Soothill, 1997]. [TOP OF PAGE]

203. **The bacteriophages. Burnet, F.M. (1934).** ***Biol. Rev. Cambridge Phil. Soc.*** **9:332-350.** [TOP OF PAGE]

204. **Bacteriophage therapy: Review of the principles and results of the use of bacteriophage in the treatment of infections (II). Eaton, M.D., Bayne-Jones, S. (1934).** ***J. Am. Med. Assoc.*** **103:1847-1853.** [TOP OF PAGE]

205. **Bacteriophage therapy: Review of the principles and results of the use of bacteriophage in the treatment of infections (III). Eaton, M.D., Bayne-Jones, S. (1934).** ***J. Am. Med. Assoc.*** **103:1934-1939.** [TOP OF PAGE]

206. **Bacteriophage therapy: Review of the principles and results of the use of bacteriophage in the treatment of infections (I). Eaton, M.D., Bayne-Jones, S. (1934).** ***J. Am. Med. Assoc.*** **103:1769-1776.** [TOP OF PAGE]

207. **Badteriophage therapy. Stout, B.E. (1933).** ***Neruol. Neurochir. Pol.*** **3:693-698.** [TOP OF PAGE]

208. **Relationship of bacteriophage to the natural and experimental diseases of laboratory animals. Colvin, M.G. (1932).** ***J. Infect. Dis.*** **51:17-29.** ["Some well controlled studies (on bacteriophage therapy), both experimental and clinical, produced results that were negative or where the observed effects were not regarded as useful." Quoted from Barrow & Soothill, 1997]. [TOP OF PAGE]

209. ***Bacteriophage in the Treatment and Prevention of Cholera.*** **Morison, J. (1932). H.K. Lewis,** ["Early (phage therapy) studies were poor and uncontrolled. For example, in one trial, claims for benefit in cholera were based on the administration of phage to all inhabitants of villages who had diarrhoea and, in another trial, on simply pouring an undisclosed

amount of phage down the village well and assessing the number of cases subjectively." quoted from Barrow & Soothill, 1997]. [TOP OF PAGE]

210. **The effect of bacteriophagy and hemotytic streptococci upon protoplasma (*Paramecium*). Rakieten, M.L. (1932). *Yale J.Biol.Med.* 4, 746-746.** Paramecia served as biological test-tubes, by first rendering them bacteriologically sterile, and then placing them in environments containing bacteria and bacteriophage. Sterile paramecia which have ingested staphylococci may be cleared of these bacteria when a small amount of a powerful bacteriophage is added to the medium containing the protozoa. When sterile paramecia are allowed to remain in the medium containing bacteriophage no evicience that the animals retained this substance in their protoplasm is obtained. The reaction between bacteria and bacteriophage does not have any observable effect on paramecium either in vivo, or in the medium surrounding them. ¶ Sterile paramecia are not affected either by the autolysates or toxic products of hemolytic streptococci. In this respect they serve no purpose as biological indicators in differentiating hemolytic streptococci. [TOP OF PAGE]

211. ***Staphylococcus aureus* meningitis: treatment with specific bacteriophage. Schless, R.A. (1932). *Am. J. Dis. Child.* 44:813-822.** [TOP OF PAGE]

212. **The kinetics of the bacterium-bacteriophage reaction. Krueger, A.P., Northrop, J.H. (1931). *J. Gen. Physiol.* 14:223-???** [TOP OF PAGE]

213. **Investigations on bacilliary dysentery in infants, with special reference to the bacteriophage phenomena. Burnet, F.M., McKie, M., Wood, I.J. (1930). *Medical Journal of Australia* 2:71-78.** [TOP OF PAGE]

214. ***The Bacteriophage and its Clinical Application.* d'Herelle, F., Smith, G.H. (1930). p.165-243. Charles C. Thomas, Publisher, Springfield,**

Illinois. [TOP OF PAGE]

215. **Use of bacteriophage filtrates in treatment of suppurative conditions: report of 300 cases. Rice, T.B. (1930).** ***American Journal of Medical Science*** **179:345-360.** [TOP OF PAGE]

216. **Choudhury, Morison (1929).** ***Indian Med. Gazette*** **64:**[TOP OF PAGE]

217. **Virus diseases of bacteria -- bacteriophagy. Bronfenbrenner, J.J. (1928).** pp. **373-414.** In In **Rivers and T.F.** (eds.), ***Filterable Viruses.*** **Williams & Wilkins, Baltimore, MD.** The inclusion of bacteriophagy or transmissible lysis of bacteria, frequently called the Twort-dHerelle phenomenon, in a discussion of filterable virus diseases may be opposed by certain workers. The fact, however, that d'Herelle believes the phenomenon to be a disease of bacteria produced by an autonomous, ultramicroscopic, corpuscular virus is sufficient reason for including a discussion of it in a book on filterable viruses. Many of the author's ideas are not in agreement with those of d'Herelle. Nevertheless, at the present time ample justification exists for considering bacteriophagy, particularly in view of the general remarks concerning filterable viruses in Chapter I. [This is a wonderful and critical review of the first decade or so of phage literature - STA]. [TOP OF PAGE]

218. **Bacteria in relation to plant diseases. Link, G.K. (1928).** pp. **590-606.** In In **Jordan, E.O. and Falk, I.S.** (eds.), ***The Newer Knowledge of Bacteriology and Immunology.*** **University of Chicago Press, Chicago.** "The phenomenon of a transmissible lytic principle (bacteriophage) has been reported by a few investigators as occurring in the plant field. This interesting but highly controversial subject has however been merely touched, and more work will have to be done before any definite conclusions can be drawn. Gerretsen and Sack, and Söhngen and Gryns report isolations of lytic principles from nodules, roots, and stems, but not from leaves of leguminous plants bearing nodules, the lytic principle being specific for the bacteria of the plants in question; also from garden and field soil, but not from heath or forest

soil. Mallmann and Hemstreet report the recovery of an inhibitory substance from cabbage decayed by fluorescent organisms, but did not demonstrate lysis. Following their work, Coons and Kotila report the recovery of a lytic principle from rotted carrots, from soil, and from river water which in low dilutions inhibited growth and in higher dilutions lysed *B. carotovorus*, *B. atrosepticus*, and *Bact. tumefaciens*. They report loss of mobility, malformation, and agglutination as characteristics of cultures treated with the lytic principle, agglutination being the first evidence of change in the organisms. Kotila and Coons also report isolation of a lytic principle from *B. atrosepticus* which when placed on potato tubers prevents the rotting normally caused by this organism. They venture the suggestion that this principle is responsible for the rapid decline of *B. atrosepticus* in the soil." (p. 601). [TOP OF PAGE]

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220. **Investigations on the blackleg disease of potato. Kotila, J.E., Coons, G.H. (1925). *Michigan Agr. Exper. Sta. Tech. Bull.* 67:**[TOP OF PAGE]

221. **Über therapeutische Versuche mit bakteriophagem Lysin bei Kindern und Saüglingen. Munter, H., Boenheim, C. (1925). *Zeitschr. F. Kinderheilk.* 39:388-???** [TOP OF PAGE]

222. **La traitment des dysentéries bacillaires par le bactériophage. da Costa Cruz, J. (1924). *Compt. Med. Rend. Soc. Biol.* 91:845-???** [TOP OF PAGE]

223. **Traitement spécifique de la fiévre typhoïde. Le Blaye, R. (1924).** p. **87-???** In **Poitiers (???)** (ed.), ***Bull.Soc.de Méd. de al Vienne*. Poitiers (???),** [TOP OF PAGE]

224. **The therapeutic value of bacteriophage in the treatment of bacillary dysentery. Spence, R.C., McKinley, E.B. (1924). *Southern M. J.***

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225. O bacteriophago en therapeutica. da Costa Cruz, J. (1923). *Brazil-med* 37:298-??? [TOP OF PAGE]

226. Le bactériophage dans le traitment de la fièvre typhoïde. Beckerich, A., Hauduroy, P. (1922). *Compt. Rend. Soc. Biol.* 86:168-??? [TOP OF PAGE]

227. *The Bacteriophage: Its Role in Immunity*. d'Herelle, F. (1922). Williams and Wilkins Co./Waverly Press, Baltimore.[TOP OF PAGE]

228. The bacteriolysant therapy of bacillary dysentery in children. Therapeutic application of bacteriolysants; d'Herelle's phenomenom. Davison, W.C. (1922). *AmJ. Dis. Child.* 23:531-??? [TOP OF PAGE]

229. Essais de thérapeutique au moyen du bactériophage. Bruynoghe, R., Maisin, J. (1921). *Compt. Rend. Soc. Biol.* 85:1120-1121. [TOP OF PAGE]

230. Le bactériophage: Son rôle dans l'immunité. d'Herelle, F. (1921). *Presse Méd.* 29:463-??? [TOP OF PAGE]

231. Le microbe bactériophage, agent d'immunité dans la peste et la barbone. d'Herelle, F. (1921). *C. R. Acad. Sci. Ser. D* 172:99-?? [TOP OF PAGE]

232. d'Herelleschen Phänomen. Otto, R., Munter, H. (1921). *Deutsche Med. Wchschr.* 47:1579-??? [TOP OF PAGE]

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contents | bacteriophage ecology group | top of page

Contact Steve Abedon (microdude+@osu.edu) with suggestions, criticisms, comments, or anything else that might help make this a better site.

1: FEMS Microbiol Lett 1997 Jun 1;151(1):65-70

M protein mediated adhesion of M type 24 Streptococcus pyogenes stimulates release of interleukin-6 by HEp-2 tissue culture cells.

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We investigated the contributions of lipoteichoic acid a protein to reversible and irreversible adhesion of group streptococci and the effects of such adhesion on releas interleukin-6. Streptococci in which lipoteichoic acid wa masked by the hyaluronate capsule were readily washed from HEp-2 cells, indicating no attachment. Unencapsul M-negative streptococci in which lipoteichoic acid was exposed were removed more slowly, indicating loose attachment. Only unencapsulated streptococci that expressed both lipoteichoic acid and M protein remaine stably adherent to HEp-2 cells throughout multiple wasl Streptococci expressing both M protein and lipoteichoi acid induced release of interleukin-6 from HEp-2 cells,